2010-1097

In the
United States Court of Appeals
For the Federal Circuit

ALCON PHARMACEUTICALS LTD. (substituted for Alcon, Inc.)
and ALCON RESEARCH, LTD.,
Plaintiffs-Appellees,

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Appellant.

Appeal from the United States District Court for the District of Delaware
in case no. 06-CV-0234, Judge Sue L. Robinson

BRIEF OF DEFENDANT-APPELLANT TEVA PHARMACEUTICALS USA, INC.

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October 4, 2013

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CERTIFICATE OF INTEREST

I, Bruce M. Gagala, Counsel for Defendant-Appellant Teva Pharmaceuticals USA, Inc., certify the following:

1. The full name of every party or *amicus* represented by me is:

Teva Pharmaceuticals USA, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Teva Pharmaceuticals USA, Inc. is the real party in interest.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or *amicus* curiae represented by me are:

The direct and indirect parent companies of Teva Pharmaceuticals USA, Inc. are: Orvet UK Unlimited, Teva Pharmaceutical Holdings Cooperative U.A., Ivax LLC (f/k/a IVAX Corporation), Teva Pharmaceuticals Europe, B.V., and Teva Pharmaceutical Industries Ltd.; Teva Pharmaceutical Industries Ltd. is the only publicly traded company that owns 10% or more of Teva Pharmaceuticals USA, Inc.

4. The names of all law firms and the partners or associates that appeared for the party or *amicus* now represented by me in the trial court or agency or are expected to appear in this Court are:

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Respectfully submitted,

/s/ Bruce M. Gagala

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TABLE OF ABBREVIATIONS

Parties:

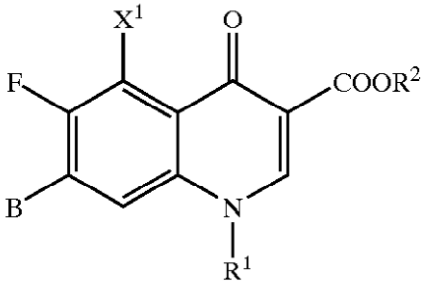
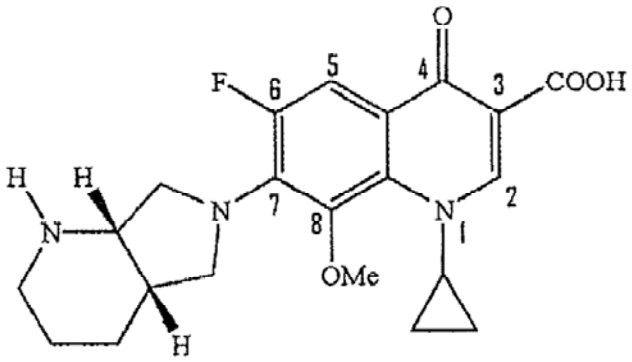
Alcon	Alcon Pharmaceuticals Ltd. (substituted for Alcon, Inc.) and Alcon Research, Ltd., Plaintiffs-Appellees
Teva	Teva Pharmaceuticals USA, Inc., Defendant-Appellant

Patent-in-Suit:

’830 Patent	U.S. Patent No. 6,716,830
’868 Application	U.S. Patent Application 10/200,868, filed July 22, 2002, which matured into the ’830 Patent
Claim 1	Claim 1 of the ’830 Patent

Defined Terms:

’942 Patent	U.S. Patent No. 5,607,942
A_	Joint Appendix page(s)
ANDA	Abbreviated New Drug Application
BAY 12-8039	“BAY 12-8039” was the name that Bayer used to refer to the compound to which the World Health Organization would later assign the International Nonproprietary Name (“INN”) “moxifloxacin hydrochloride.”
District Court	United States District Court for the District of Delaware
Examiner	United States Patent and Trademark Office Examiner of the ’830 Patent

FDA	United States Food and Drug Administration
Formula(I)	 (I) [Wherein A, B, X^1, R^1, and R^2 of Formula(I) are omitted for brevity]
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
INN	International Nonproprietary Name, published by the World Health Organization
INN-moxifloxacin	
MIC	MIC refers to "minimum inhibitory concentration," and, as between two compounds, the one with a lower MIC value is more active in inhibiting the growth of a particular pathogen.
Orange Book	The FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations"

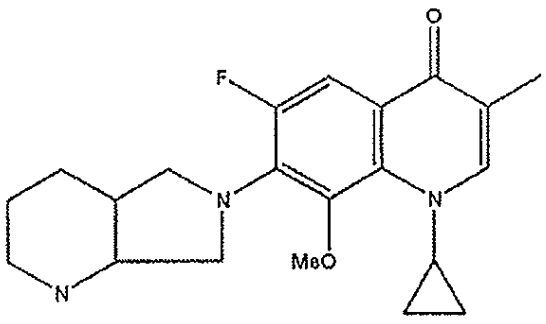
PDR	Physicians' Desk Reference
POSA	Person having ordinary skill in the art
Structure(S)	 [(S)]"
Teva's ANDA Product	Teva's proposed ophthalmic solution, as defined in ANDA No. 78-073
wt.%	weight percent

TABLE OF AUTHORITIES

Cases

Statutes

STATEMENT REQUESTING ORAL ARGUMENT

Teva Pharmaceuticals USA, Inc. requests oral argument in this appeal.

STATEMENT OF RELATED CASES

This is an appeal from the United States District Court for the District of Delaware in Civil Action No. 06-cv-00234-SLR, with which Civil Action No. 07-cv-00195-SLR was consolidated. Counsel for Teva are not aware of any other appeal in or from the same proceedings in the District Court that was previously before this or any other appellate court.

Other than this appeal, counsel for Teva are aware of Civil Action No. 11-cv-00587-SLR (D. Del. filed July 1, 2011 and consolidated with case nos. 12-cv-00973-SLR and 12-cv-00960), Civil Action No. 11-cv-00293-SLR (D. Del. filed April 7, 2011), and *Inter Partes* Review case no. IPR 2013-00012 (Patent Trial and Appeal Board filed October 4, 2012), all of which involve the ’830 Patent at issue in the present action. Counsel for Teva are unaware of any other pending case that will directly affect or be directly affected by this Court’s decision.

Although it purports to relate to a different patent, the docket sheet for Civil Action No. 13-cv-01230-SLR (D. Del.) references related Civil Action No. 11-cv-00587-SLR (D. Del.) and Civil Action No. 11-cv-00293-SLR (D. Del.). A second *Inter Partes* Review, case no. IPR 2013-00015 (Patent Trial and Appeal Board), relates to U.S. Application No. 12/611,510 and to U.S. Patent No. 7,671,070, a continuation of the ’830 Patent at issue in the present appeal.

JURISDICTIONAL STATEMENT

The District Court had jurisdiction under 28 U.S.C. §§ 1331, 1338. This Court has jurisdiction pursuant to 28 U.S.C. §1295(a).

STATEMENT OF THE ISSUES

1. Whether the District Court erred in "correcting" a "mistake" in an express definition of a claim term in the patent specification where neither the "mistake" nor its "correction" are apparent from the claims, specification, and prosecution history.

2. Whether the District Court erred as a matter of law in construing Claim 1.

3. If the District Court's claim construction is correct, whether the District Court erred in concluding that Claim 1 is not invalid as obvious where the only differences between the prior art and the claimed invention were a concentration range and a pharmaceutically acceptable vehicle clearly suggested by the prior art.

I. INTRODUCTION

The single claim asserted in this patent suit under the Hatch-Waxman Act concerns a topical ophthalmic pharmaceutical composition comprising "moxifloxacin" at specified concentrations in a particular pharmaceutically acceptable vehicle. The inventors expressly and unambiguously defined "moxifloxacin" in the patent by a chemical formula. Teva's accused product concededly does not contain "moxifloxacin" so defined.

The patentee, Alcon, argued that the unambiguous definition of moxifloxacin was a "mistake" and that "moxifloxacin" is really an entirely different chemical. Neither the existence of this "mistake" nor its "correction" is apparent from the patent or its prosecution history. Alcon never sought correction of the patent under 35 U.S.C. §255. Nor could it obtain statutory correction because the "correct" chemical was neither disclosed in the application nor examined by the PTO. The decisions of this Court governing both claim construction and claim correction obliged the District Court to take the inventors at their definitional word and find that Teva's ANDA Product does not infringe.

However, the District Court disregarded all pertinent principles of claim correction and construction and impermissibly rewrote the claim-in-suit to cover a composition that was not even disclosed in the patent, much less examined by the PTO. Doubtless, the District Court believed that it was saving a valuable patent

from destruction resulting from what Alcon insisted was an innocent clerical error. But the District Court overlooked what this Court must not: because inventors are free to be their own lexicographers, their definition must be accepted by the public and enforced by the courts, even if the inventors made an honest mistake and even if that mistake makes the claim anomalous or inoperable. It is only when the mistake and its correction are manifest on the face of the patent that a correction is permissible, and that is indisputably not the case here.

Moreover, the District Court's misguided attempt to save the patent from the careless drafting of the inventors was ultimately futile because the "corrected" claim is obvious. Moxifloxacin, as erroneously redefined by the District Court, was an antibiotic well-known in the prior art, and known to be suitable for ophthalmic formulation. Teva proved, and the District Court found, that one of skill in the art would have known that the substitution of moxifloxacin for similar compounds in prior art ophthalmic compositions would have been effective. Indeed, that is all the inventors themselves surmised, without experimentation and without even possessing any moxifloxacin.

The District Court rejected Teva's obviousness defense based on a suggestion in the prior art that moxifloxacin might be less effective against a particular ocular pathogen than a particular prior art compound. Because the inventors identified their goal as the development of a more effective treatment for

"a key ophthalmic pathogen," the District Court concluded that one of skill in the art would not be motivated to select moxifloxacin for use in a topical ophthalmic formulation. But the District Court erred as a matter of law in characterizing the obviousness inquiry in terms of compound selection and in failing to recognize, as the decisions of this Court clearly instruct, that obviousness may be shown if the prior art suggests *any* reason for a skilled artisan to develop the claimed invention, not merely the reason that motivated the inventors. The undisputed record gives many such reasons, and the District Court erred as a matter of law in failing to find the claim-in-suit obvious. Its judgment must be reversed.

II. STATEMENT OF THE CASE

This case arises out of an ANDA that Teva filed seeking approval of a drug product generic to Alcon's Vigamox®, a topical ophthalmic solution. The '830 Patent is listed in the Orange Book for Vigamox®. Teva's ANDA contained a certification under 21 U.S.C. §355(j)(2)(A)(vii)(IV).

In 2006, Alcon sued Teva for patent infringement under 35 U.S.C. §271(e)(2). A337-41. Teva denied infringement and asserted invalidity. A456-60. The parties stipulated that, if Teva's ANDA Product does not contain "moxifloxacin" as that term is used in Claim 1, then Teva's ANDA Product does not infringe Claim 1. A713 ¶58; A643 ¶26.

On October 20, 2009, the District Court entered judgment for Alcon, ruled that Teva's ANDA Product infringes Claim 1, and that the '830 Patent is not invalid. A51-52. Teva's appeal was filed on November 19, 2009 (A2518), docketed on December 2, 2009 (A2520), but deactivated on December 7, 2009 (A60) due to Alcon's motion to amend the judgment (A2511-17). On August 5, 2010, the District Court granted-in-part Plaintiffs' motion and ordered the FDA not to approve Teva's ANDA Product before expiration of the '830 patent. A53-58. On July 22, 2013, this appeal was reactivated. A61-62.

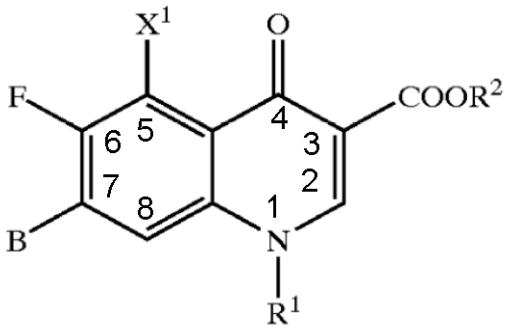
III. STATEMENT OF FACTS

A. The '830 Patent

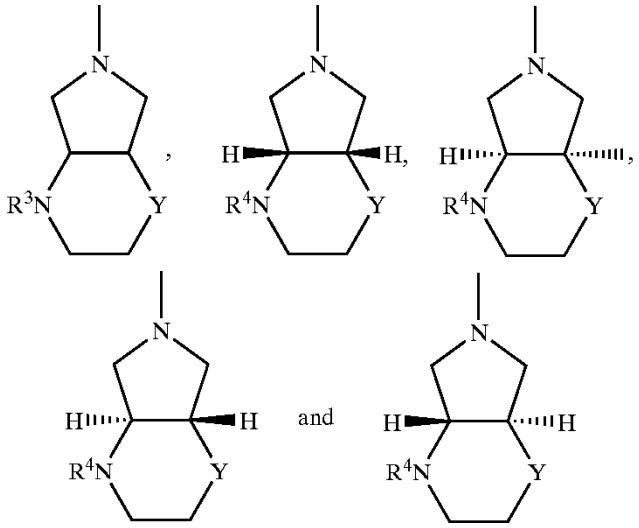
1. The Claims and Specification

The '830 Patent purports to be directed to ophthalmic, otic, and nasal compositions containing a "potent new class of antibiotics" and the use of these compositions to treat such infections. A66(2:6-12). The specification states that this new class has the structure of Formula(I) (with ring positions numbered for ease of reference):

(I)



A66(2:51-60). R^2 is defined as "H, C_1 to C_3 alkyl (optionally substituted by OH, halogen or NH_2), or 5-methyl-2-oxo-1,3-dioxol-f-yl-methyl" (A67(3:1-3)), and B is a *Markush* group of a racemate or mixture of enantiomers (or stereoisomers) (A1208:24-A1209:12) and each of four enantiomers:



A67(3:4-20). The specification also purports to define a substituent "A" as "CH, CF, CCl, C-OCH_3, or N" (A66(2:62)), but Formula(I) does not indicate where substituent "A" is supposed to go. Substituents R^3, R^4 and Y are also defined.

However, the *claims* of the '830 Patent make no reference to this class of compounds but rather recite topical ophthalmic pharmaceutical compositions in which "moxifloxacin" is the active ingredient. Claim 1, the only claim at issue, recites:

> A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt.% and pharmaceutically acceptable vehicle therefor.

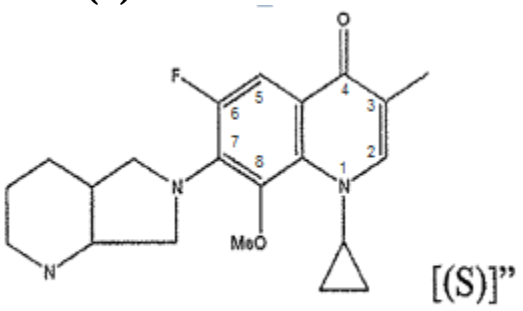
A69(7:29-32). The specification identifies "moxifloxacin" as Structure(S) (A67(3:36-48)) (*see* Table of Abbreviations and p. 9 *infra*). The specification also states: "Further details regarding the structure, preparation, and physical properties of Moxifloxacin and other compounds of Formula(I) are provided in U.S. Pat. No. 5,607,942." A67(3:49-51). But the '830 Patent refers to no specific portion of the '942 Patent, which is 100 columns long (A2676-2728) and which the District Court recognized covers "numerous" compounds (A21) and, according to Alcon, covers a "billion compounds" (A1132:17; A1179:1-11; A2432; A2434-35).

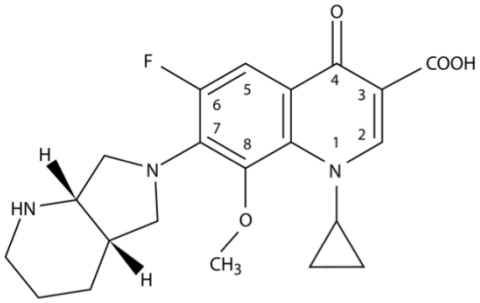
Alcon's chemistry expert, Dr. Taylor, acknowledged that Structure(S) is outside the structure of general Formula(I) because Formula(I) does not provide for a methoxy group (a methyl group bound to oxygen) at position 8, A1229(14-17) or for the methyl substituent at the 3-position, as is depicted for Structure(S). A1229:14-19.

Alcon argued that "moxifloxacin" was meant to be defined as the chemical ultimately given the INN[1] name "moxifloxacin" (A6100-6101; A1158:20-A1159:11; A1221:17-23; A1235:10-A1236:12). But Structure(S) is a different chemical:

[1] The INN proposes and recommends internationally-acceptable names for pharmaceutical compounds. A1156:21-25.

Structure(S) **INN-Moxifloxacin**





Methyl group at 3-position
No chirality shown

Carboxyl group at 3-position
S,S enantiomer

The specification of the ’830 Patent also includes four prophetic “Examples” of compositions comprising “moxifloxacin.” A68(6:34)-A69(7:23). The inventors presented these “Examples” with no experimentation whatsoever, by basing them on formulations of prior art ophthalmic antibiotics and essentially replacing the names of the active ingredients in such formulations with the word “moxifloxacin”. A1295:7-A1296:18; A1303:15-A1304:16; A1308:24-A1310:13; A1313:15-18; A1747:2-A1748:10; A2671-A2674.

2. The Prosecution History

The Parties agree that priority date for the ’830 Patent is September 30, 1998, the filing date for two U.S. provisional applications (A1721:4-9; A64 (Related U.S. Application Data); A5221-33; A1672:9-19).

As filed, Claim 1 of the application that led to the ’830 Patent recited a genus of compounds, including their chemical structures. *Compare* A3508-10 *with* A66(2:49)-A67(3:35). The claim was rejected as anticipated by the ’942 Patent.

A4751-54; A4764. In response, Alcon amended the application to claim the moxifloxacin composition of Claim 1 (A4760) and persuaded the examiner that the amended subject matter was patentable over the '942 Patent. A4764-4765.

At no point during prosecution did Alcon tell the Examiner which of the "numerous," "billions" of compounds disclosed by the '942 Patent was "moxifloxacin." Alcon told the examiner that the "only portions of the '942 Patent having any relevance to the present invention are seen in the second paragraph in column 54 and the fifth paragraph in column 56" (A4765). The "portions" do not refer to "moxifloxacin" or any other compound. The only compound identified to the examiner as "moxifloxacin" was Structure(S) found in the specification.

3. The Level of Ordinary Skill Includes Skill in Formulation

The '830 Patent states that the invention is "directed to the provision of topical antibiotic pharmaceutical compositions" and that the claimed pharmaceutical composition is "specially formulated." A66(1:13-16; 2:38-40). As the District Court noted, "the aim of the '830 Patent is, ultimately, to formulate a composition for ophthalmic use." A18. To achieve that goal requires a formulator's experience. A1332:20-A1333:6. Alcon's experts agreed that skill in the relevant art includes some skills in formulation. A1945:11-16; A1946:6-7; A2101:18-A2102:3 (Dr. Zhanel); A1510:1-13; A1511:7-9; A1545:16-19 (Dr. Alfonso). However, pharmaceutical formulation development is not within the

skill of the inventors (A1773:4-13), nor within the skill of an ophthalmologist (A1545:12-15; A1585:16-A1586:13). Similarly, a microbiologist would rely on the skill of a formulator to develop a pharmaceutical composition (A2083(1003:6-10); A2101(1077:19)-A2102(1078:3)).

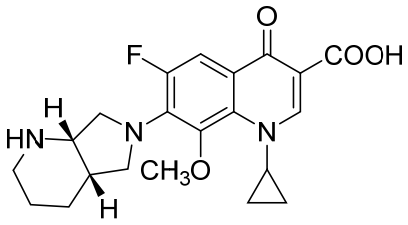
Although the named inventors of the '830 Patent had formal education in microbiology (A7; A17), they did not perform any microbiological tests (or, indeed, any tests at all) of any compound described as "moxifloxacin" until well after the priority date. A1673:2-8. Importantly, the inventors' experience at Alcon supplemented their formal education. They enjoyed the benefit of Alcon's institutional expertise in ophthalmic antibiotics (including Ciloxan®, the leading brand of ophthalmic antibiotics on the market at the time) (A2524-27; A1768:11-A1769:4). Indeed, the development of Alcon's commercial ophthalmic moxifloxacin formulation that is said to embody Claim 1 (A1773:4-13)—the "special formulation" that characterizes the claimed inventions—was accomplished by "a whole bunch of [Alcon] formulators whose job is to do that" (A1773:9-10), none of whom were named inventors of the '830 Patent.

B. Prior Art Ophthalmic Fluoroquinolone Formulations

1. Bayer's '942 Patent

The prior art '942 Patent discloses and claims the antibiotic that would later become known as INN-moxifloxacin, although it neither employs the term

"moxifloxacin" nor refers to any compound as "moxifloxacin." A2690; A1287:23-A1288:17; A1342:21-A1343:3. Claim 1 of the '942 Patent claims the compound with the chemical structure of INN-moxifloxacin:



A2727(98:55-65). Claim 3 recites "[a]n antibacterial composition comprising an antibacterially effective amount of a compound or addition product thereof according to claim 1 [*i.e.*, INN-moxifloxacin] and a diluent." A2728(99:21-23).

According to the '942 Patent, the disclosed compounds are active against a "broad spectrum" of microorganisms and can treat and/or prevent local diseases caused by Gram-negative bacteria such as *Pseudomonas aeruginosa* ("*P. aeruginosa*") and Gram-positive bacteria such as *Staphylococcus aureus* ("*S. aureus*"). A2705:34-39; A2705:45-67. Both bacteria were recognized in 1998 as ocular pathogens. A2705(53:48-54:22); A1491:23-A1492:15.

The '942 Patent discloses pharmaceutical formulations containing "one or more compounds according to the invention," in "addition to non-toxic, inert pharmaceutically suitable excipients." A2705(54:47-52). It discloses that "[p]ossible suitable formulations are... emulsions, ointments or drops" and that "[o]phthalmological and dermatological formulations... eye ointments... can be

used for local therapy." A2705(54:22); A2706(56:24-30). It specifically mentions use of the compounds to treat "eye infections" (A1278:16-A1279:10); A2705(54:22), and teaches that they can be present in pharmaceutical formulations in a concentration of about 0.1 to 99.5 wt.%, preferably about 0.5 to 95% by wt.%. A2706(56:7-10).

The '942 Patent also discloses a "pharmaceutically acceptable vehicle" for solutions, ointments, and suspensions (among others), including water, the primary vehicle commonly used in ophthalmic solutions. A1291:15-A1292:5; A2669. The '942 Patent states that the disclosed compositions (including ophthalmic formulations) also can contain customary excipients, and it gives examples. A2706(55:50-59); A1291:15-A1292:5.

2. Prior Art Formulations of Ciprofloxacin and Ofloxacin

Fluoroquinolones were a recognized class of broad spectrum antibacterial agents in September 1998. A1268:10-17. Ciprofloxacin ("the gold standard" (A2045:15)) and ofloxacin—both fluoroquinolones—were state-of-the-art treatments for ocular bacterial infections. A1558:8-22; A1667:12-19; A1964:8-23; A1302:8-17 A2540; A2541-44; A2549; A2550-53. They were the active ingredients in: Ciloxan® ophthalmic solution and ointment (A1293:9-12; A1566:1-17; A1964:8-23; A1302:8-17) and Ocuflox® ophthalmic solution, respectively. A1558:8-22; A1667:12-A1668:6; A1964:8-23. Moxifloxacin was

also known to be a fluoroquinolone antibacterial agent in 1998. A1601:10-13; A6882-85.

(a) Ophthalmic Ciprofloxacin (Ciloxan®)

The FDA approved Ciloxan® ophthalmic solution in 1990 (A2540; A1294:3-10); it is prior art to the '830 Patent, as is its 1996 PDR monograph. A2541-44. Ciloxan® solution contained 0.35 wt.% ciprofloxacin hydrochloride, and a pharmaceutically acceptable vehicle of purified water (A1295:1-2), excipients, and a preservative. A2541-44; A2671; A1293:13-18; A1294:11-A1295:2. The formulation for Ciloxan® ophthalmic solution is virtually identical to Example 1 of the '830 Patent, except that "moxifloxacin" is substituted for "ciprofloxacin." A2671; A1295:22-A1297:19.

Ciloxan® also was approved as an ointment (A2549). The formulation for Ciloxan® ophthalmic ointment is virtually identical to Example 3 of the '830 Patent, except that "moxifloxacin" is substituted for "ciprofloxacin." A1313:15-A1304:16; A2673.

(b) Ophthalmic Ofloxacin (Ocuflox®)

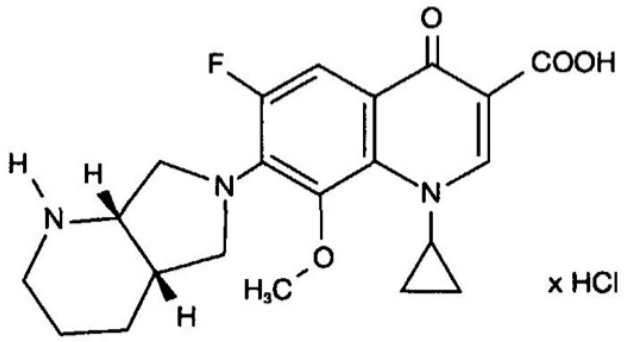
The FDA approved Ocuflox® as of 1995 (A2550-53); Ocuflox® is prior art to the '830 Patent, as is its 1995 PDR monograph. A2550-53. Ocuflox® included 0.3 wt.% ofloxacin as the active agent in a pharmaceutically acceptable vehicle of

purified water (A2550-53; A1319:25-A1320:8), and other excipients. A1319:25-A1320:8.

C. Known Properties of Moxifloxacin as of September 30, 1998

1. Prior Art Disclosed that Moxifloxacin HCl Had Potent Activity Against Bacterial Ophthalmic Pathogens

As of the priority date, much was known about moxifloxacin. At a 1996 conference, Bayer presented an abstract ("Petersen Abstract"), which disclosed that a fluoroquinolone compound that Bayer called "BAY 12-8039" exhibited "potent antibacterial activities against both Gram-negative and Gram-positive bacteria and anaerobes." A6021-23; A1322:17-A1323:3. In 1997, Bayer published a poster identifying BAY 12-8039 as having the following structure:



A6845. BAY 12-8039 is a hydrochloride salt of INN-moxifloxacin. The INN referred to this compound as "moxifloxacin HCl" (A1158:20-A1159:20; A1221:17-23; A6100-01), and this brief will do so as well. The poster also disclosed how to make moxifloxacin HCl and comparative data demonstrating that moxifloxacin HCl was more active against *S. aureus* than either ciprofloxacin or

ofloxacin, and more active against *P. aeruginosa* than ofloxacin. A6845; A2675; A1576:18-A1578:6; A1982:4-9; A2335.

2. Prior Art Disclosed that Moxifloxacin HCl Could Be Formulated into a Solution Suitable for Ophthalmic Use

The Petersen Abstract disclosed that moxifloxacin HCl has a solubility of 24 mg/ml in water at 25 °C. A6021-23; A6845; A1322:21-A1324:18; A1611:22-A1612:21. Dr. Allen, Teva's pharmaceutical expert (A1265:24-A1266:18), testified without contradiction that this disclosure would have taught a POSA that moxifloxacin HCl could be made into a solution for ophthalmic use, and that such teaching would motivate a POSA to substitute "moxifloxacin" for other fluoroquinolones in known ocular formulations with the expectation that the resulting composition would also be an effective ophthalmic antibiotic. A1271:2-19; A1299:8-16; A1322:13-A1324:7; A1344:2-8. The District Court specifically found this to be so. A30-31.

3. Moxifloxacin HCl Was Known To Have Pharmacokinetic Characteristics Favorable for Ophthalmic Use

By September, 1998, Bayer had reported that moxifloxacin HCl "is rapidly bactericidal and effectively penetrates extravascular tissue[2], including lung tissue." A6378; A1612:22-A1614:13. Alcon's pharmacokinetics expert, Dr. Mitra, acknowledged on cross-examination that it would have been expected

[2] The eye is an extravascular tissue. A1614:14-20.

for moxifloxacin (BAY 12-8039) to penetrate the eye more readily than gold-standard ciprofloxacin and comparably to state-of-the-art ofloxacin. A1894:14-20; A1895:16-18. Alcon offered no contrary evidence.

4. Moxifloxacin HCl Was Known To Be Highly Tolerated in Patients

During prosecution of the '942 Patent, the inventors submitted the declaration of a Bayer researcher, Dr. Bremm, to the PTO, which presented data comparing moxifloxacin HCl with two other fluoroquinolones. Dr. Bremm declared that moxifloxacin HCl "compares favorably with [the other compounds] in terms of its antimicrobial activity. However, [moxifloxacin HCl] is 30- to 70-fold better… in terms of its phototoxicity. This means that [moxifloxacin HCl] has a much better pharmacological profile than do the [other compounds]." A2950. In a second declaration, Dr. Bremm stated:

> Indeed, of all the fluoroquinolones that we have investigated, the compound of claim 25 [moxifloxacin hydrate or salt thereof] is the *best* tolerated that we have ever seen.

A2960 (emphasis in original); A1282:23-A1283:24.[3]

The prior art also contained peer-reviewed articles by Bayer scientists disclosing that moxifloxacin HCl "is a compound with a low level of toxicity," with single doses of up to 800 mg having been tolerated in human patients

[3] These declarations became prior art upon the issuance of the '942 Patent in 1997. *See Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1379-80 (Fed. Cir. 2006).

"without serious side effects." A2568. This level of exposure is much higher than exposure from an ophthalmic dose. Exposure to Alcon's Vigamox® product three times daily results in systemic exposure to moxifloxacin HCl at a level 1,600 to 1,000 times *lower* than exposure from even a 400 mg oral dose. A1639:17-A1640:10. Other prior art publications pointed out that moxifloxacin HCl had excellent safety and tolerability and favorable pharmacokinetics. A2571; A6378-83; A1629:3-A1630:18. By 1997, it was known that moxifloxacin HCl had entered Phase II clinical trials (A6845, A1324:19-A1325:21), a further indication that the compound was not regarded as toxic. A1325:9-A1326:7. Alcon offered no contrary evidence.

5. Moxifloxacin HCl Had a Superior Resistance Profile

By 1998, Bayer scientists had published papers demonstrating that moxifloxacin HCl exhibited a more favorable resistance profile than other fluoroquinolones. For example, in 1996, Bayer reported that resistance against moxifloxacin HCl developed much more slowly in Gram-positive bacteria than did resistance to ciprofloxacin (A6880; A1619:24-A1621:25), and that resistance to moxifloxacin HCl emerged less rapidly than to ciprofloxacin in both *P. aeruginosa* and *S. aureus*. A6878; A2093(1045:23)-A2094(1047:2).

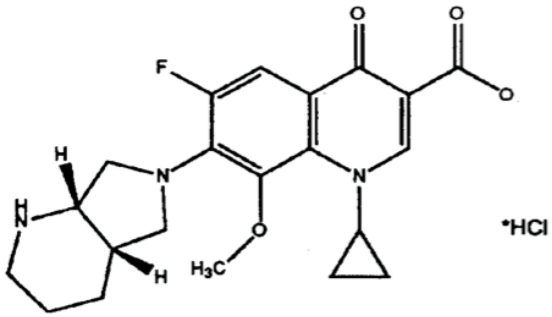
In September 1998, Bayer reported that, with respect to *S. aureus* and as compared with older fluoroquinolones (such as ciprofloxacin and ofloxacin),

moxifloxacin HCl was less influenced by known mutations within the genetic *loci* involved in fluoroquinolone resistance. A6885; A1624:21-A1625:13. The publication notes that moxifloxacin HCl was active against ciprofloxacin-resistant *S. aureus* strains that had become resistant to ciprofloxacin (MIC 0.5-2 mg/L). A6883. Again, Alcon offered no contrary evidence.

6. Alcon's Development of Vigamox®

Alcon began selling ciprofloxacin-based Ciloxan® products (a solution (eye drops) and an ointment) (A2540) in the mid-1990s, and Ciloxan® became the "gold standard" (A2045:8-17) for ocular bacterial infections. But in the late 1990's Alcon faced market pressure due to the impending expiration of patent protection for ciprofloxacin (A2528; A1770:9-A1772:2) and actively sought to identify compounds for possible development into new patent-protected topical ophthalmic formulations. A1667:12-A1668:6.

Based on Bayer's presentations at scientific meetings, Alcon's Dr. Stroman identified moxifloxacin HCl as one of 10-15 compounds of interest. A1670:2-20; A1671:10-14; A1739:22-A1740:1; A6845. He requested a sample of moxifloxacin HCl in February 1998 (A6842; A1745:15-22; A1747:9-14), identifying (i) the compound as "BAY 12-8039," (ii) the source of the compound as Bayer, (iii) "Several posters at 1997 ICAAC" as the basis for the request, and (iv) describing the compound as:



Alcon did not receive a sample for nearly a year, and well after the priority date, which marked the latest date by which the inventors claim to have conceived the claimed compositions. A1747:15-17. Alcon's two provisional patent applications ostensibly disclosing the claimed invention were thus filed before Alcon had performed *any* testing or analysis on moxifloxacin HCl. A1748:1-10; A1759:7-15.

In September 1998, before Alcon received its first moxifloxacin HCl sample, Dr. Abshire, a co-inventor of the '830 Patent, wrote to his Alcon colleagues:

> …[T]hese newer quinolones represent the only family of antibacterial agents that are most readily available to [Alcon] immediately to develop for ophthalmic use, and of these, moxifloxacin would definitely be our choice because of the recent developments with Bayer.... Dr. Stroman and I agree that we should obtain moxifloxacin and develop it for ophthalmic use. All of the aforementioned newer quinolones have very similar in vitro spectra. Some data show that moxifloxacin is somewhat more active than the others.

A2523.

Ultimately, Alcon's formulators—not the named inventors—developed what would become Vigamox® ophthalmic solution. Vigamox® consists of moxifloxacin HCl, 0.5 wt.% and particular excipients in water. A2532-35; A1273:1-11; A1642:9-11. The FDA has approved Vigamox® only "for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: [list omitted]." A2535; A1640:17-23. Absent from this list is *P. aeruginosa*. Vigamox® does not contain Structure(S), and the '830 Patent does not describe the Vigamox® formulation. A1773:1-3; A2083(1004:15-17).

IV. SUMMARY OF THE ARGUMENT

Claim 1 recites a pharmaceutical composition of "moxifloxacin," and the '830 Patent unambiguously defines "moxifloxacin" as Structure(S). A67(3:36-48). There is no indication in the specification or file history that the Examiner of the '830 Patent considered the patentability of a pharmaceutical composition with the different structure of INN-moxifloxacin. Faced with no evidence in the '830 Patent or its prosecution history that identified "moxifloxacin" with INN-moxifloxacin, Alcon resorted to expert testimony and other extrinsic evidence to persuade the District Court that a POSA would disregard the '830 Patent's disclosure, surmise that Structure(S) contained typographical errors, and read the claim term "moxifloxacin" to refer to INN-moxifloxacin.

However, the District Court erred as a matter of law in so construing the term "moxifloxacin" in Claim 1. That construction required a correction of the patent that the decisions of this Court did not permit because neither the *existence* of any error in the patent's definition of moxifloxacin nor *the correction* of that error is apparent from the intrinsic evidence.

As a matter of law, the District Court was obliged to take the inventors at their word as lexicographers and to construe "moxifloxacin" in Claim 1 as the inventors themselves defined it, *i.e.*, as Structure(S). Upon such a construction, the parties have stipulated there is no infringement; therefore, the judgment must be reversed.

If the District Court's claim construction stands, however, then the District Court erred in not finding Claim 1 obvious. The District Court found that the only differences between the prior art and Claim 1 is a specific weight concentration and a pharmaceutically acceptable vehicle. But both the concentration and pharmaceutically acceptable vehicle for a fluoroquinolone topical ophthalmic composition were disclosed or clearly suggested by the prior art. The District Court erred in determining a POSA as being a microbiologist or M.D. with training in ophthalmology and not a pharmaceutical formulator. The '830 Patent is manifestly directed to the formulation of a known compound into a pharmaceutical composition, precisely, the art of a formulator. The evidence at trial clearly

established that the claimed composition would have been obvious to a formulator of ordinary skill.

The District Court further erred by ruling that the only factor that could motivate a POSA to develop the claimed pharmaceutical composition was the inventors' stated motivation to *select* a medication that was more effective than existing ophthalmic antibiotics against particular pathogens. The law is clear that any motivation suggested by the prior art will support an obviousness defense, not just the motivation of the inventors. The District Court further erred as a matter of law in framing the obviousness inquiry in terms of a selection invention because moxifloxacin was known, and the "invention" is for a composition, not a chemical. Further, because such superior effectiveness is not an element of the claim-in-suit, and because the undisputed evidence clearly and convincingly established alternative motivations to combine prior art elements to develop the claimed composition, the claim-in-suit was obvious.

V. ARGUMENT

On its face, the patent defines the term "moxifloxacin" in Claim 1 as the chemical compound of Structure(S). Alcon contends Structure(S) contains a typographical error and that the "real" compound of Claim 1 is INN-moxifloxacin. The dispute is central to Alcon's infringement claim. The parties stipulated that, if

"moxifloxacin" in Claim 1 is Structure(S), then Teva's ANDA Product does not infringe Claim 1.

A. The District Court Erred as a Matter of Law in Correcting the Patent's Definition of "Moxifloxacin"

1. Standard of Review

Claim construction is a question of law that this Court reviews *de novo*. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc). What the applicant or PTO understood a claim term to mean is irrelevant to that question, "except as documented in the prosecution history." *Id.* at 985. Whether an ostensible "mistake" in a patent is correctible by a district court also is a question of law. *Superior Fireplace v. Majestic Prods. Co.*, 270 F.3d 1358, 1369 (Fed. Cir. 2001); *Central Admixture Pharmacy Servs., Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1353 (Fed. Cir. 2007).

2. The District Court Erred in Disregarding the Inventors' Lexicography in Defining "Moxifloxacin"

"[Claim] terms are not always afforded their ordinary meaning." *SkinMedica, Inc. v. Histogen, Inc.*, No. 2012-1560, 2013 WL 4487603, at *7 (Fed. Cir. Aug. 23, 2013). Patentees have "flexibility to imbue new or old terms with a different meaning than they would otherwise have to a person of ordinary skill in the art." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004); *see Honeywell Int'l, Inc. v. Universal Avionics Sys.*

Corp., 493 F.3d 1358, 1361 (Fed. Cir. 2007). No express statement that the patentee is departing from the plain and ordinary meaning of a claim term is required. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Astrazeneca AB, Aktiebolaget Hassle, KBI-E, Inc. v. Mutual Pharm. Co.*, 384 F.3d 1333, 1339 (Fed. Cir. 2004) (lexicography does not require "rigid formalism"); *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) (Intrinsic evidence may show the patentees gave a term "an unconventional meaning" and the "specification may define claim terms 'by implication'").

It follows from the unquestioned power of the patentee to ascribe unconventional or special meanings to claim terms, that the public has both the right and the obligation to take the inventors at their definitional word. Any other rule would undermine the public notice function of patents in defining the "metes and bounds" of the patentee's right to exclude.

The detailed description of the invention in the '830 Patent provides an explicit definition of the claim term "moxifloxacin" (*i.e.*, Structure(S)). A67(3:36-48) ("Moxifloxacin has the following structure: [Structure(S)]"). Because the inventors chose to be lexicographers, it is this definition that must be applied. Instead, the District Court noted discrepancies between Structure(S) and Formula(I) and inferred that Structure(S) (and not Formula(I)) contains

typographical errors: "Notably absent from this representation of moxifloxacin is the 3-position carboxylic acid. Likewise, the '830 Patent omits any graphical depiction of moxifloxacin's stereochemistry." A11 (citation omitted). The District Court purported to resolve the typographical errors by redefining Structure(S) to include components from Formula(I). A66(2:51-60).

Initially, one of the discrepancies noted by the District Court does not suggest an error at all. The omission in Structure(S) of a graphical description of a particular enantiomer is not a departure from Formula(I). The first candidate for substituent "B" in Formula(I) signals a racemate or mixture of enantiomers (or stereoisomers) but not a particular enantiomer and certainly not the S,S-enantiomer. Because no specific enantiomer or stereoisomer is identified, a POSA would logically assume that moxifloxacin, as defined by the inventors, is also a racemate or mixture of enantiomers or stereoisomers, not that the absence of a graphical depiction of a particular enantiomer is an error.

But even if one assumes that a POSA would conclude that discrepancies between Structure(S) and Formula(I) evidence errors in Structure(S), nothing in Formula(I) or in the '830 Patent or in its prosecution history points to the specific corrections that the District Court made:

- Formula(I) does not show the location of substituent "A," which the specification defines as "CH, CF, CCl, C-OCH_3, or N" (A66(2:62)), or that

substituent "A" is a methoxy (–OCH_3). As such, one simply cannot determine how Structure(S) should incorporate substituent "A." A1229:14-17.

- The specification defines substituent "B" as "selected from the group consisting of" a racemate or mixture of enantiomers (or stereoisomers) (flat structure at upper left) and each of four enantiomers (A67(3:4-20)), leaving no reason to choose the S,S-enantiomer. As Structure(S) lacks an indication of stereochemistry, it is consistent with the first possible alternative for "B," which connotes a racemate or mixture of enantiomers (or stereoisomers). Certainly nothing in the patent or prosecution history points to any of the four identified stereoisomers as applicable to Structure(S).
- At column 3, the '830 Patent's disclosure of the "flat" structure as one of five possibilities for substituent "B" of Formula(I) shows a substituent of R3 linked to a nitrogen atom within the six-member ring. Structure(S), which also has a "flat" structure configuration of what Alcon contends corresponds to substituent "B," does not indicate what is bonded to the nitrogen, which Dr. Taylor testified would indicate hydrogen (A1209:22-A1210:9). However, for Formula(I), R3 cannot be hydrogen (A67:24-26).
- At the 3-position of Formula(I), the specification defines R^2 as "H, C_1 to C_3 alkyl (optionally substituted by OH, halogen or NH_2), or 5-methyl-2-oxo-

1,3-dioxol-f-yl-methyl." A67(3:1-3). Only by referring to extrinsic evidence could the District Court find that R^2 is hydrogen in moxifloxacin (A4), because the intrinsic evidence ('830 prosecution history) includes references showing quinolones whereby R^2 has substituents other than hydrogen. A3582-83; A3641-42; A3744-45; A3795; A3797-99; A3919; A3921-22; A4137-39; A4194-95; A4231; A4285; A4287; A4456; A4461-62; A4470; A4613; A4626.

- At the 3-position of Structure(S), the '830 Patent's specification defines the substituent as CH_3, not $COOR^2$, and absent extrinsic evidence, there is no reason to replace CH_3 in Structure(S) with $COOR^2$ of Formula(I), even if one could discern which candidate for R^2 was intended.

In short, the intrinsic evidence supplies no basis whatever to "correct" Structure(S) *to make it INN-moxifloxacin as* opposed *to some other embodiment of Formula(I)*.

It does not matter that, as the District Court found, the conventional meaning of "moxifloxacin" to a POSA was INN-moxifloxacin. When inventors define their invention unconventionally, with words or figures, patent law requires that they be taken at their word. For example, in *International Rectifier Corp. v. IXYS Corp.*, 361 F.3d 1363, 1373 (Fed. Cir. 2004), the inventor used the word "annular" to describe structures that were not circular or curved—the ordinary meaning of

"annular"—but polygonal (a square and a hexagon). This Court found that "the patentee acted as his own lexicographer" in using the term "annular." *Id.* Here, the inventors deviated from what the District Court found to be the "ordinary and customary meaning" of moxifloxacin as INN-moxifloxacin by using Structure(S) to define moxifloxacin instead. Even if a POSA would recognize the disparity between Structure(S) and INN-moxifloxacin, a POSA, *aware that inventors are free to assign unconventional meanings to terms*, would take the inventors at their word.

This is true even if the patent as written is anomalous. In *Chef America Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1373 (Fed. Cir. 2004), the patentee claimed a process for producing a dough product that included as one of its steps heating the dough "to a temperature in the range of about 400º F. to 850º F." Because a POSA would know that a dough product heated to such a high temperature would be unusable, the patentee asked that the claim be "construed" to refer to the temperature *at which* the dough would be heated, not the temperature *to which* it would be heated. This Court declined to rewrite an unambiguous, if wildly implausible, claim. *Id.* at 1374. Similarly here, the '830 Patent's definition of moxifloxacin should control even if a POSA would be surprised by the non-standard definition of "moxifloxacin."

The District Court's reliance on Alcon's expert testimony and other extrinsic evidence to construe the claim violated basic claim construction principles established by this Court. It elevated the most suspect form of extrinsic evidence—"generated at the time of and for the purpose of litigation"—over the intrinsic record. Such extrinsic evidence is "less significant than the intrinsic record in determining the legally operative meaning of claim language." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). As this Court has cautioned, "extrinsic evidence consisting of expert reports and testimony… generated at the time of and for the purpose of litigation… can suffer from bias that is not present in intrinsic evidence." *Id.* at 1318. "[U]ndue reliance on extrinsic evidence poses the risk that it will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history,' thereby undermining the public notice function of patents." *Id.* at 1319. The District Court strayed far beyond the permissible use of experts for "background on the technology" or "how an invention works." *Id.* at 1318; *see also Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008) ("A court may look to extrinsic evidence so long as the extrinsic evidence does not contradict the meaning otherwise apparent from the intrinsic record."). The District Court relied on Alcon's expert, who testified in substance that a POSA would not take

the inventors at their word. Such testimony is irrelevant because as a matter of law, the inventors' word governs.

The District Court also erred by relying on the alleged "mutual understanding between the PTO and the inventors" and the "testimony of Dr. Stroman." A21-22. A district court cannot rely on the subjective intent of the applicant or PTO to construe a patent, *Markman*, 52 F.3d at 985; *Superior Fireplace*, 270 F.3d at 1375 (patentee's assertion "that the examiner and the patentee both understood that the claim only required a single rear wall" was "completely without merit").

The District Court further erred by its reliance on the '942 Patent as being "incorporate[ed] by reference" (A21) into the '830 Patent. Whether and to what extent material has been incorporated by reference into the '830 Patent is a question of law. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). "To incorporate material by reference, the host document (i.e., the '830 Patent) must identify *with detailed particularity* ***what*** specific material it incorporates and *clearly indicate* ***where*** that material is found in the various documents." *Id.* (emphases added). It was incumbent on the inventors to identify in the '830 Patent which of the "billions" of compounds disclosed in the '942 Patent was considered "moxifloxacin," and specifically where within the '942 Patent's 100 columns the disclosure of moxifloxacin was to be found. The simple

reference of the '830 Patent's disclosure to the '942 Patent in only the most general terms does not remotely satisfy the standard for incorporating by reference the '942 Patent. The District Court's failure to apply the appropriate standard is legal error. Viewed simply as an exercise in claim construction, the District Court's construction of "moxifloxacin" was plainly wrong.

3. The District Court Erred in Exceeding its Power to Correct Errors in a Patent as Part of Claim Construction

At a more fundamental level, however, the issue here is not limited to claim *construction* at all. The District Court and the parties all recognized that the '830 Patent clearly defined "moxifloxacin" as Structure(S). Under the guise of claim construction, the District Court found that the inventors made a mistake in their definition and engaged in claim *correction*. But this Court has severely restricted the power of district courts to correct patents, and the District Court's ruling manifestly ignores those restrictions.

In general, the risk of a drafting mistake falls on the patentee. *Southwest Software, Inc. v. Harlequin Inc.*, 226 F.3d 1280, 1296 (Fed. Cir. 2000) ("[I]t does not seem to us to be asking too much to expect a patentee to check a patent when it is issued in order to determine whether it contains any errors that require the issuance of a certificate of correction."). Congress created only a very limited process for correcting an applicant's mistakes in an issued patent:

> Whenever a mistake of a clerical or typographical nature, or of minor character, which was not the fault of the Patent and Trademark Office, appears in a patent and a showing has been made that such mistake occurred in good faith, the Director may, upon payment of the required fee, issue a certificate of correction, *if the correction does not involve such changes in the patent as would constitute new matter or would require re-examination*. Such patent, together with the certificate, shall have the same effect and operation in law on the trial of actions for causes thereafter arising as if the same had been originally issued in such corrected form.

35 U.S.C. §255 (1999) (emphasis added).

The power of courts to "correct" typographical errors in a patent in the course of claim construction is even narrower. *Novo Indus., L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354 (Fed. Cir. 2003). "Congress [did not] intend[] that the district courts have the authority to correct any and all errors that the PTO would be authorized to correct." *Id.* at 1356. Unlike the PTO, district courts can only correct "obvious minor typographical and clerical errors in patents" (*id.* at 1357), but then only where those minor errors are: "(1) not subject to reasonable debate based on consideration of the claim language and the specification and (2) the prosecution history does not suggest a different interpretation of the claims." *Id.* at 1357. Any other errors in patents may be corrected, if at all, only by the PTO. *Id.*

A mistake that, if corrected, "broadens a claim is not a 'mistake of... minor character' subject to correction under 35 U.S.C. §255." The PTO can make broadening corrections of clerical or typographical errors, but "only where it is clearly evident from the specification, drawings, and prosecution history how the

error should be appropriately corrected." *Superior Fireplace*, 270 F.3d at 1372. That limitation on the PTO's power is necessary to preserve the *public notice* function of patents. *Id.* at 1371 ("a broadening correction [under §255] would leave the public without effective notice, without the constraint of a two-year time bar, and without the hope of intervening rights" of §§251, 252); *id.* at 1372-73.

Novo Industries makes it clear that the power of district courts to correct patents is even narrower and does not extend *at all* to broadening corrections. 350 F.3d at 1356-57. The power of district courts is limited to correcting only "obvious minor" errors, *id.* at 1357, and a *broadening* correction is not, as a matter of law, of "minor character." *Superior Fireplace*, 270 F.3d at 1375; *Novo Indus.*, 350 F.3d at 1356 ("broadening corrections" are beyond a court's limited authority). The concern for public notice and for protecting the public against a broadening correction is "implicit" in Section 255.

Whether a court's correction of a patent has impermissibly broadened a claim is a question of law. *Central Admixture*, 482 F.3d at 1353. And the law is that a correction is broadening if the corrected patent "covers territory" the uncorrected patent did not. *Id.* The correction covers more territory if it is more likely that the accused product infringes when it might not have infringed before the correction. *Id.* at 1351.

Moreover, a district court has the power to correct a "clerical or typographical" error *only* where it is *clearly evident from the intrinsic record* "how to correct" that error. *Central Admixture*, 482 F.3d at 1353; *id.* at 1355 n.6 ("it must be '*clearly evident* from the specification, drawings, and prosecution history how the error should appropriately be corrected") (emphasis in original). "[E]ven where the mistake is apparent, it may not be clear how the mistake should be corrected." *Superior Fireplace*, 270 F.3d at 1370. The Court in *Superior Fireplace* ruled that if either the existence of the purported error or its correction are not apparent based on the public record, the patent cannot be corrected. *Id.*

The District Court observed *none* of these restrictions. First, the existence of the "error" in Structure(S) was not apparent from the intrinsic evidence. It was not a "misspelling[] that leave[s] no doubt as to the word which was intended; 'frane' instead of 'frame,' for example." *Id.* Rather, the purported error is a formula for a chemical that was not shown to be chemically impossible. It is, in other words, "spelled correctly" and "reads logically in the context of the sentence." *Id.* *See Group One Ltd. v. Hallmark Cards, Inc.*, 407 F.3d 1297, 1303 (Fed. Cir. 2005) ("The error here is not evident on the face of the patent."); *Central Admixture*, 483 F.3d at 1353-55 (error to "correct" a patent by replacing "osmolarity" with "osmolality" because both words are chemical terms that fit the context). As

shown above (*supra*, pp. 26-28), it is not at all apparent from the discrepancies between Structure(S) and Formula(I) that the former contains a mistake.

Moreover, the effect of the "correction" is to broaden Claim 1. The parties stipulated and the District Court acknowledged that, if "moxifloxacin" in Claim 1 is "Structure(S)," then Teva's ANDA Product does not infringe Claim 1, but it does infringe if "moxifloxacin" is INN-moxifloxacin. A16; A713 ¶58. Because Teva's ANDA Product infringes Claim 1 only under the "corrected" claim construction, the correction impermissibly broadened Claim 1. *Central Admixture*, 482 F.3d at 1353; *Novo Indus.*, 350 F.3d at 1356.

Nor is the District Court's "correction" apparent from the intrinsic evidence. Even if a POSA inferred an error in Structure(S) to the extent it did not conform to Formula(I), there is no way to discern from the patent or prosecution history which Formula(I) embodiment the inventors meant Structure(S) to be. One simply cannot determine from the patent which substituents "A" and "B" should have been used or even where substituent "A" should go. A1229:14-A2-30:3; A1224:10-A1225:7; A1229:20-A1230:3. Alcon's expert admitted that the many alleged "errors" could be "corrected" in various ways. A1225:16-24; A1228:12-21; A1229:20-A1231:16.

The '830 Patent's prosecution history does not provide any additional guidance for "correcting" the ostensible "error" in the patent. During prosecution,

applicants cancelled claims to the "genus" of Formula(I) and limited them to "moxifloxacin." A4760. In traversing the rejection based on the '942 Patent, applicants did not identify which of the many compounds disclosed in the '942 Patent was "moxifloxacin," instead referring the Examiner to portions of the '942 Patent "as the only portions that have any relevance…." A4765. The '830 Patent was then allowed. A4774.

The many legal restrictions to correcting a patent ignored by the District Court are not mere technicalities, but serve important functions. They preserve the limitations that Congress imposed on the PTO's statutory power to correct patents. In *Novo Industries*, this Court ruled that Congress authorized the PTO to make broadening corrections only prospectively:

> [T]o allow the district court to correct such errors would effectively write the nonretroactivity provisions out of … [35 U.S.C. §] 255. The district court always would apply its own corrections retroactively in the action before it, unlike certificates of correction issued by the PTO, which apply only in actions brought after the certificate of correction is issued.

Novo Indus., 350 F.3d at 1356-57; *Superior Fireplace Co.*, 270 F.3d at 1380 ("[I]t strikes us as an illogical result to allow the patent holder... to sue an alleged infringer for activities that occurred before the issuance of the certificate of correction."). They preserve the public notice function of patent claims.

Moreover, to allow the correction of an error where the error and its correction are not both immediately apparent on the face of the patent opens the

door to patenting inventions that were never actually examined. Title 35 U.S.C. §255 permits the correction of an applicant's errors only when "the correction does not involve such changes in the patent as would constitute new matter or would require reexamination." If the correction introduces "new matter" not considered by the examiner, then one can have no confidence that the examiner actually determined that the "corrected" claim was in fact patentable. Here, there is no way to infer that the examiner examined Claim 1 with the formula for INN-moxifloxacin as opposed to Structure(S) in mind.

The District Court erred as a matter of law in "correcting" the '830 Patent to cover compositions with INN-moxifloxacin. The claims are restricted to compositions with Structure(S). Because it is undisputed that Teva's ANDA Product does not contain Structure(S), the judgment of infringement must be reversed.

B. If "Moxifloxacin" Is INN-Moxifloxacin, then the Claim Is Obvious

The '830 Patent reflects scant inventive activity. Alcon scientists merely substituted moxifloxacin for the active ingredient in prior art formulations involving structurally similar compounds. The evidence at trial clearly and convincingly established that such a substitution was obvious. The District Court rejected this clear inference from the evidence only by defining a POSA and

identifying the motivations that would affect POSAs in a manner inconsistent with the decisions of this Court.

1. The Law of Obviousness

Obviousness is a question of law that this Court reviews *de novo*, based on underlying factual questions that are reviewed for clear error following a bench trial. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd*, 719 F.3d 1346, 1354 (Fed. Cir. 2013); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

A patent is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a [POSA] to which said subject matter pertains." 35 U.S.C. §103(a) (Nov. 29, 1999). The primary factors that bear on obviousness include (1) the scope and content of the prior art, (2) the differences between the claims and the prior art, (3) the level of ordinary skill in the art, and (4) secondary considerations of non-obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) ("*KSR*"); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Media Techs. Licensing, LLC v. Upper Deck Co.*, 596 F.3d 1334, 1337 (Fed. Cir. 2010).

The obviousness analysis requires "an expansive and flexible approach." *KSR*, 550 U.S. at 415. The question is "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* at

418. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 419-20. A POSA may be able to fit together the teachings of multiple pieces of prior art, like a puzzle – this is still evidence of obviousness. *Id.* at 420; *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009).

A reason for one of ordinary skill in the art to modify or combine the prior art may be provided by "any need or problem known in the field… and addressed by the patent." *KSR*, 550 U.S. at 420. "There is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come *from* the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997) (emphasis in original) (citation omitted); *KSR*, 550 U.S. at 418; *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), *abrogated on other grounds*, *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000).

Ultimately, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417. There need not be "precise teachings directed to the specific

subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

2. Claim 1 and the '942 Patent Differ Only in the Specific Weight Concentration Range Recited in Claim 1

Independent Claim 1 recites a topical ophthalmic pharmaceutical composition comprising: (1) moxifloxacin; (2) at a concentration range of 0.1-1.0 wt.%; and (3) a pharmaceutically acceptable vehicle. A69(7:29-32). The District Court credits the prior art '942 Patent with disclosing the compound found by the District Court to be "moxifloxacin."[4] A21. The District Court made the following findings:

- The '942 Patent discloses use of the compounds identified therein for a "topical ophthalmic pharmaceutical composition" (A24);
- The '942 Patent discloses (by structure and systematic (IUPAC) name) and claims the "structure which would later receive the INN moxifloxacin" or a pharmaceutically useful hydrate or salt thereof (A6 n.9; A21; A24-25);
- The '942 Patent's use of the structure and IUPAC name was "[b]ecause WHO had not yet determined the INN 'moxifloxacin'" (A6 n.9);

[4] Teva's obviousness argument assumes that "moxifloxacin" as used in Claim 1 of the '830 Patent is INN-moxifloxacin. If the Court rules that "moxifloxacin" as used in Claim 1 is Structure(S), then it need not address the obviousness argument.

- The ’942 Patent specification discloses the “efficacy” of what would later be given the name INN-moxifloxacin to “a broad antibacterial spectrum against Gram-negative and Gram-positive bacteria” (A6); and
- The ’942 Patent discloses that what would later be given the name INN-moxifloxacin, is a fluoroquinolone (A4; A6 n.9).

None of this was disputed. However, the District Court concluded that the ’942 Patent did not disclose “the concentration range of 0.1 to 1 wt% or ‘a pharmaceutically acceptable vehicle.’” A25-A27. Thus, according to the District Court’s analysis, the only difference between the ’942 Patent and the claimed invention—the first *Graham* factor—is the concentration range and pharmaceutically acceptable vehicle recited in Claim 1.

As explained below, the District Court was wrong at least as to the “vehicle,” because the ’942 patent does disclose a vehicle, and the purported differences were plainly suggested by the prior art and would have been obvious to a POSA. But first we turn to the District Court’s erroneous identification of the level of ordinary skill in the art.

3. The Level of Ordinary Skill in the Art Must Include the Skills of a Pharmaceutical Formulator

As one of its “Conclusions of Law” (A15), the District Court ruled that a POSA would be a person with a Ph.D. in microbiology, the training of the inventors themselves, or an M.D. with training in ophthalmology (A17), but would

not be a formulator. A18. In so ruling, the District Court misapplied the standards adopted by this Court for identifying the level of ordinary skill in the pertinent art in *Daiichi Sanko Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). Specifically, the District Court focused much too heavily on the first factor — the educational level of the inventors — while unduly discounting the other factors and without appreciating that the inventors made little use of their own professional training as microbiologists in conceiving the claimed *composition*.

Daiichi identified the following factors to guide the identification of the level of skill in the pertinent art: "(1) the education level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." 501 F.3d at 1256. The Court stressed that this list of factors is not exhaustive. *Id*.

The District Court placed far too much emphasis on the first factor. The inventors are microbiologists, but what was novel about the invention—taking a known antibiotic and formulating it into an ophthalmic composition—had little to do with microbiology. Indeed, the embodiments of the claimed pharmaceutical composition identified in the patent's examples were concededly "invented" based on prior art formulations involving other compounds and substituting moxifloxacin. The actual work of developing the specific therapeutically effective

formulation of moxifloxacin that Alcon sells as Vigamox® — the development of a suitable weight concentration and vehicle — was assigned to Alcon formulators, who were not the inventors.

The District Court gave short shrift (or no shrift at all) to the other factors which uniformly point to the need for a POSA to have skill in pharmaceutical formulation. As to the second factor, the "problems" associated with devising a concentration range and suitable vehicle for formulating a known antibiotic into an ophthalmic pharmaceutical composition are problems for which pharmaceutical formulators, not microbiologists, or ophthalmologists, are trained, as Alcon's experts acknowledged. A1945:11-16; A1946:6-7; A2101:18-A2102:3 ; A1510:1-13; A1511:7-9; A1545:16-19; A1585:16-A1586:30. As to the third factor, the pertinent "prior art solutions" to the problem of devising a topical ophthalmic composition of moxifloxacin are prior art formulations of other fluoroquinolones into which the inventors mechanically substituted moxifloxacin.

As to the fourth *Daiichi* factor, the formulation problems to which Claim 1 is directed are usually solved quickly, as it is generally not difficult to formulate known antibiotics into ophthalmic formulations. A1332:20-A1333:6. Indeed, the undisputed evidence is that *for formulators*, the development of such dosage forms is "routine[]." A1330:24-A1331:16; A1332:24-A1333:6.

As to the fifth *Daiichi* factor, while it is not difficult for skilled formulators to develop new ophthalmic dosage forms, formulation technology itself is sophisticated, and outside the experience of most microbiologists. Alcon's microbiology expert, Dr. Zhanel, testified that he and his colleagues might be able to prepare certain "microbiological" formulations of ophthalmic antibiotics, but that he would not be comfortable if such formulations were placed in the eyes, as a genuine "pharmaceutical" formulation would be. A2080(992:11-993:22); A2083(1004:3-14). Dr. Zhanel admitted that preparation of a pharmaceutical formulation, suitable for patient use, required expertise in pharmaceutical formulation. A2083(1003:6-10); A2101(1077:18)-A2102(1078:3).

As to the sixth factor, the District Court ignored that the inventors were not "active workers in the field" of pharmaceutical formulation. While they may have conceived that moxifloxacin could be used in an ophthalmic formulation in concentrations and using vehicles similar to other fluoroquinolone formulations, they were not active formulators. It was Alcon's formulators who did the work of proving the inventors' speculation — for that was all it was before they even possessed any moxifloxacin — that moxifloxacin would work just as well as other fluoroquinolones to treat at least some eye infections. Alcon's expert in microbiology admitted that microbiologists did not have the skill necessary to prepare pharmaceutical formulations. A2101(1077:18)-A2102(1078:3).

All of the *Daiichi* factors, save possibly the first, clearly suggest that pharmaceutical formulation skills are critical to the art pertinent to the claimed invention, and the first factor under the particular circumstances of this case does not undermine that suggestion.

Here—where the invention is a particular formulation of a known drug—the POSA includes a formulator. The District Court clearly erred in deciding that the skills of the relevant art were those of a microbiologist or ophthalmologist and not those of a pharmaceutical formulator. This Court in *Daiichi* recognized that because the invention in that case was directed toward the development of a method of using a specified drug to treat ear infections, the pertinent skills included those of a pharmaceutical formulator with experience in ear medicines. *Daiichi*, 501 F.3d at 1257. So here, where the invention is directed to the formulation of a specified prior art drug as a topical ophthalmic pharmaceutical composition, the pertinent skills include those of a pharmaceutical formulator as well.

4. The Use of Moxifloxacin to Treat Eye Infections Was Taught in the '942 Patent

The '942 Patent disclosed the use of moxifloxacin to treat eye infections, the only medical or microbiological aspect of the claimed invention. A1283:25-A1284:13; A2705(54:22). Formulating moxifloxacin into a topical ophthalmic composition was the only "problem" solved by the '830 Patent. A66(2:38-45); A1347:5-23. However, prior art formulations had solved the problem of

formulating fluoroquinolones into ophthalmic formulations. Ciloxan® (ciprofloxacin) and Ocuflox® (ofloxacin) were considered state-of-the-art in 1998. Ciloxan® and Ocuflox® formulations represented favorable, commercially-acceptable prior art solutions to the "problem" of formulating ophthalmic compositions of a known fluoroquinolone antibiotic. A1271:2-A1272:4; A1293:6-18; A1319:14-20; A1577:21-22; A1765:14-A1766:11; A2540; A2541-44; A2549; A2550-53; A6838-41.

According to Dr. Allen's uncontradicted testimony, the therapeutic effectiveness of exchanging moxifloxacin for the previously-known active antibiotics in prior art topical ophthalmic formulations was completely predictable from the '942 Patent (A1283:25-A1284:13), its file history (A1284:6-18), the Bayer ICAAC poster (A1327:7-A1329:5), Ciloxan® solution (A1296:19-A1297:3), Ciloxan® ointment (A1304:20-A1305:9), and Ocuflox® (A1320:9-25). A POSA would have expected that an ophthalmic composition comprising moxifloxacin HCl in place of ciprofloxacin HCl in Ciloxan® solution (as in Example 1 of the '830 Patent) would have antibacterial properties and would be a suitable topical ophthalmic pharmaceutical composition. A1296:19-A1297:19. Similarly, a POSA would reasonably expect exchanging moxifloxacin for the ciprofloxacin in Ciloxan® ointment (as in Example 4 of the '830 Patent) would result in an effective topical ophthalmic antibiotic. A1271:2-19; A1304:20-

A1305:3. Unrebutted testimony establishes that a POSA would expect that exchanging "moxifloxacin" for the ciprofloxacin and ofloxacin in these prior art formulations would be expected to result in topical ophthalmic compositions possessing antibacterial properties. A1304:20-A1305:9,23-A1306:8; A1320:9-25; A1321:25-A1322:12. Indeed, the District Court specifically found that a topical ophthalmic composition of moxifloxacin HCl would "predictably possess" antibacterial properties. A31.

5. A "Pharmaceutically Acceptable Vehicle" Was Disclosed in the Prior Art

The District Court's finding that the '942 Patent did not disclose a "pharmaceutically-acceptable vehicle" was clearly erroneous. The '942 Patent states that the compositions disclosed (including ophthalmic formulations) can contain customary excipients, and provides examples of excipients. A2706(55:50-59); A1291:15-A1292:5. *Compare* A2705(54:65-67) ("pharmaceutically suitable excipients are to be understood as solid, semi-solid or liquid diluents, fillers, and formulation auxiliaries of all types"), A2705(54:47-52), and A2706(55:1-5) *with* A68(5:47-51) ("compositions are typically administered to the affected ophthalmic, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable amount of an ointment, gel or other solid or semisolid composition"). Dr. Allen testified that the '942 patent discloses water

as a vehicle (A1288:6-8; A1291:15-A1292:5), and water is the most common vehicle for ophthalmic formulations. A1291:15-A1292:5; A2669.

Prior art references Ciloxan® and Ocuflox® (discussed above; A1300:13-17; 1305:10-22; A1321:18-21) also unquestionably disclosed "pharmaceutically acceptable vehicles" in ophthalmic pharmaceutical composition. Nothing in the '830 Patent suggests that such vehicles would not work equally well with moxifloxacin. Even Alcon acknowledged:

> There likewise is no dispute that the *only* difference between the prior art and the claimed invention is the active ingredient — the state of the art compositions contained cipro[floxacin] and ofloxacin, while the claimed compositions contain moxifloxacin.

A2392 (emphasis in original; citing A1295:7-A1313:18; A1319:10-1322:5; A2671-A2674).

6. The Claimed Concentration Range Was Obvious

The District Court correctly found that the '942 Patent disclosed INN-moxifloxacin. A6, A14, A21-22, A24-25. However, the District Court concluded that the '942 Patent did not disclose the concentration range of 0.1 to 1 wt.% even though the '942 Patent's range is 0.1 to 99.5 wt.%, preferably about 0.5 to 95 wt.%, which encompasses the range claimed in the '830 Patent. A25-A27. The District Court erred. It was undisputed that a POSA would know that the concentrations of the active fluoroquinolone in ophthalmic preparations are at the low end of the range disclosed in the '942 Patent based on formulation experience

and prior art, such as Ciloxan® and Ocuflox®. Moreover, any fine-tuning of the concentrations for particular products was a matter of routine experimentation (A1330:24-A1331:16; A1332:24-A1333:6), and thus not patentable. *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation."). As explained below, on the undisputed evidence, the claimed range was obvious.

(a) The Claimed Range Was Obvious to a Formulator

The claimed concentration range was obvious to a formulator in view of Ciloxan® and Ocuflox® ophthalmic compositions, in which, respectively, the concentration for ciprofloxacin was 0.35 wt.% and for oflocacin was 0.3 wt.%. A POSA would have expected concentrations under 1 wt.% to be particularly applicable to ophthalmic formulations. A1290:1-A1291:4; A2541-44; A1293:1-18; A2250-53; A1301:11-A1302:2; A1319:10-A1320:8. Nothing in the prior art taught away from using the 0.1-1% wt.% range of the prior art compounds in a moxifloxacin formulation, nor is there evidence that this range is associated with any unexpected results.

Formulating moxifloxacin ('942 Patent) in an ophthalmic composition within the concentration range of other fluoroquinolone ophthalmic preparations (Ciloxan® and Ocuflox®) is precisely the kind of combination of prior art elements that courts have often found to be obvious. *KSR*, 550 U.S. at 416-21.

According to Dr. Allen's undisputed testimony, ophthalmic formulations were known typically to have concentrations of less than 1.0 wt.% of the active ingredient. A1290:1-A1291:4. Prior art Ciloxan® and Ocuflox® were typical of these: they were ophthalmic compositions with antibiotics from the same pharmaceutical class as "moxifloxacin" at concentrations less than 1.0 wt.%. A1290:1-16; A1293:13-18; A1301:11-A1302:2; A1319:6-A1320:8. The substitution of moxifloxacin hydrochloride from the '942 Patent and/or Petersen poster or abstract for the fluoroquinolone compounds in these commercial topical ophthalmic formulations was not only obvious it was "foolish not to do." A1271:2-19; A1322:13-A1323:10; A1299:8-16; A1344:2-8. The prior art would have guided and motivated a POSA precisely to make the substitution. *Bayer Schering*, 575 F.3d at 1350.

Such substitutions were a "routine" part of the pharmaceutical formulator's techniques, undertaken with the expectation that similar concentrations and formulations of similar drugs would behave similarly. A1330:24-A1331:16; A1332:20-A1333:6. Therefore, a POSA would have understood the '942 Patent in view of the formulations taught by Ciloxan® (0.35 and 0.3 wt.%) and Ocuflox® (0.3 wt.%) (A2541-2544; A2550-53; A6838-41) to suggest the use of moxifloxacin in a concentration within the range 0.1 to 1.0 wt.%, in an ophthalmic composition. This is a "textbook case of when the asserted claims involve a combination of

familiar elements according to known methods that does no more than yield predictable results." *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008).

(b) Market Pressure Further Evinces the Obviousness of Claim 1

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 US at 407-408. Alcon faced market pressure because Bayer's patent on ciprofloxacin, the active ingredient in Ciloxan®, was about to expire. Alcon did not invent a new antibiotic. Instead, Alcon sent Dr. Stroman to the 1997 ICAAC to identify potential successors to ciprofloxacin. Dr. Stroman identified moxifloxacin HCl—which Bayer had already identified as a formidable antibiotic—as one of 10-15 compounds of interest, but he was only able to obtain five or six for testing. A1670:2-.A1671:17. Dr. Stroman's use of one of a limited number of antibiotics in a prior art formulation of another fluoroquinolone evinces the obviousness of Claim 1 under the rubric of *KSR*.

(c) Claim 1 Is Obvious Because the Claimed Range Overlaps the Prior Art

"[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range," the claimed range is presumptively obvious. *Tyco Healthcare Group LP v. Mutual Pharm. Co.*, 642 F.3d 1370, 1372-73 (Fed. Cir. 2011); *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) ("Similarly, if prior art discloses a portion of the claimed range, the entire claim is invalid. Courts do not rewrite the claims to narrow them for the patentee to cover only the valid portion."); *see also Daiichi*, 501 F.3d at 1259 n.4.

In *Alcon Research*, the prior art reference rendered claims obvious because its 0.0001%-0.01% "range overlaps with" the claimed 0.0001%-5% range. *Id.* at 1367, 1369 ("disclosure of overlapping concentrations, even if for a different purpose, meets these claim limitations"). In *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012), claims were held invalid as obvious where the prior art range of 0.375-0.75 mEq/mg "falls within the" claimed range of 0.1-2.5 mEq/mg, and the prior art range of 63-6300 mg "overlaps with" the claimed range of 1000-2000 mg. *Id.* at 1353-54. In *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286 (Fed. Cir. 2013), a claim was held obvious where the limitation of "about 0.2%" beta-blocker was within the prior art range of "from 0.02 to 2.0%" and the limitation of "about 0.5%" alpha-agonist was within the prior art range of "from 0.01 to 3.0%."

Under the legal standard as applied in *Tyco*, *Santarus*, and *Allergan*, the claimed concentration range is presumptively obvious because there is overlap with ranges and values disclosed in the prior art. The District Court acknowledged overlap between the prior art ranges disclosed by Ciloxan® (0.30-0.35 wt.%), Ocuflox® (0.3 wt.%), and the '942 Patent (0.1-99.5% and 0.5-95%) on the one hand, and the claimed range of 0.1-1.0 wt.% on the other. A13; A25. Moreover, unrebutted testimony proves that a POSA would have understood the *ophthalmic* formulations of the '942 Patent to have a concentration of less than 1.0 wt.% in view of the concentrations taught by Ciloxan® and Ocuflox®. A1290:1-A1291:4; A1293:13-18; A1301:11-A1302:2; A1319:6-A1320:8; A2541-44; A2250-53.

Because any variance from the *precise* concentration range recited in Claim 1 is the only real difference between Claim 1 and the prior art, the claim is presumptively obvious. There was no evidence at trial to rebut that presumption. *See Tyco*, 642 F.3d at 1373; *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). There was no evidence of any teaching away from a topical ophthalmic composition moxifloxacin in the range of 0.1-1.0 wt.%. The evidence clearly established that a POSA would have expected concentrations under 1.0 wt.% to be particularly applicable to ophthalmic formulations. A1290:1-A1291:4; A1293:1-18; A1319:10-A1320:8; A2541-44, A2250-53. Accordingly, this Court should reverse the District Court's conclusion of non-obviousness.

7. The District Court Erred as a Matter of Law in Requiring Teva to Prove a POSA Would Have Selected Moxifloxacin as a Lead Compound

The District Court erred as a matter of law in framing the obviousness inquiry in terms of the selection of moxifloxacin for a new composition. The cases on which the District Court relied are "lead compound" cases in which the defendant argued that a new compound was obvious. The question in such cases is whether a POSA would be motivated to select the prior art compound as a "lead compound" for modification to produce a claimed compound. By focusing on a "hundred compounds" and "thousands of abstracts" considered by Dr. Stroman, the District Court erroneously treated the selection of moxifloxacin as a "lead compound" for a pharmaceutical composition with moxifloxacin *itself* as the active ingredient. A8; A17 n.21; A18; A29-31; A41.

The lead compound doctrine is inapplicable here because moxifloxacin was not a new compound and the "selection" of moxifloxacin is not "the inventive aspect of the patent," as the District Court found. A18. Rather, the "invention" claimed in the '830 Patent is a formulation—formulating prior art moxifloxacin in an ophthalmic composition with the claimed concentration range. The selection of moxifloxacin for ophthalmic use was suggested by the '942 patent. Accordingly, the proper question in this case was whether it would have been obvious to formulate a known fluoroquinolone with known antibacterial properties similarly,

if not identically, to the known (and successful) formulations of other known fluoroquinolones (e.g., Ciloxan® and Ocuflox®. The answer is plainly yes, but the District Court applied the wrong legal standard and came to an erroneous conclusion.

The District Court's reliance on lead-compound selection cases ignores this Court's analysis in *Daiichi*. In *Daiichi*, this Court held that a claim covering the use of a known fluoroquinolone in a method of treating ear infections was obvious in light of a prior art use of another fluoroquinolone to treat ear infections. 501 F.3d at 1258-59.

8. The District Court Erred as a Matter of Law in Limiting the Relevant Motivation to Unclaimed "Efficacy and Resistance" Properties Toward Unclaimed "Ophthalmic Pathogens"

(a) The '942 Patent Claimed a Pharmaceutically Acceptable Moxifloxacin Composition

The District Court found that the only possible motivation for a POSA to make the claimed invention was to develop a compound that was more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance:

> The '830 patent provides that the field of treating and preventing ophthalmic infections was concerned with developing "improved compositions... based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens." [A66(1:49-53).] One skilled in the art would understand that this

> disclosure referred to the sight-threatening pathogens *Pseudomonas aeruginosa* and *Staphylococcus aureus* and the standard treatment of such by CILOXAN® and OCUFLOX®. (A1480-86) [sic] A person of ordinary skill in the art would also understand that a resistance problem existed with respect to the treatment of these two key ophthalmic pathogens, and that this issue was critical to the development of a viable new treatment. It was evident in 1998 that any potential ophthalmic treatment which did not improve upon the efficacy and resistance issues would be considered impractical and worthless to one skilled in the art.

A31-32 (ellipsis in original). From this the District court inferred that a POSA would not be motivated to select moxifloxacin to combine it with prior art elements to derive claim 1.

But the District Court erred in two respects. The District Court erred first in overlooking the prior art teachings that moxifloxacin was in fact highly effective against those two pathogens. The District Court further erred as a matter of law in ignoring other clear motivating considerations.

The prior art taught that high concentrations of moxifloxacin HCl inhibited *aeruginosa*, that moxifloxacin has a high aqueous solubility at or near physiological pH, and thus, could be formulated at high concentrations. A Bayer abstract (A6021-23) and poster (A6845) taught that moxifloxacin has favorably low MIC values for a wide spectrum of bacteria and taught it has a high solubility. This information indicated to a POSA that sufficient moxifloxacin could be supplied to the site of infection to meet or exceed ofloxacin's MIC value for *Pseudomonas aeruginosa*. A1271:2-19; A1322:13-A1323:10; A1577:1-16.

Dr. Stroman admitted, and no Alcon experts disputed, that moxifloxacin was known to be active against bacteria associated with ocular infections. A1759:16-A1760:16.

Beyond that, the evidence clearly established a motivation for a POSA to devise the claimed invention. The '942 Patent claimed a pharmaceutically acceptable moxifloxacin composition. A POSA would be motivated to formulate moxifloxacin into an ophthalmic composition because:

- Moxifloxacin was known to be active against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both ophthalmic pathogens (A2335; A2675; A6864-81; A1576:18-A1578:6; A1578:19-A1580:5; A1594:2-13; A1759:16-A1760:16; A2554-57; A6088-93);
- Moxifloxacin's activity exceeded ofloxacin, which was one of the "standards of care" for ophthalmic infections (A2335; A2675; A1558:8-14; A1576:18-A1578:6; A1982:4-9; A6845);
- Moxifloxacin was well-tolerated in humans (A2336-37; A2568; A2571; A6845; A1324:19-A1325:21; A1325:9-A1326:7; A1627:2-A1628:20; A1629:3-A1630:18);
- Moxafloxacin was more active that ciprofloxacin against staphylococci and streptococci and active against strains of those pathogens that were resistant

to cirprofloxacin (A6864-81; A1578:19-A1580:5; A1594:2-13; A1759:16-A1760:16);

- Moxifloxacin's bacterial resistance exceeded ciprofloxacin (the other state-of-the-art treatment for ophthalmic infections), and moxifloxacin was active against *Staphylococcus aureus* strains that were resistant to other fluoroquinolones (A2335-36; A6866; A6882-83; A6885; A1558:8-22; A1578:19-A1580:5; A1619:24-A1621:25; A1624:21-A1625:13; A2093(1045:23)-A2094(1047:2); A2110(1113:8-1114:4); A2554-57; A2558-61; A6080-87; A6088-93; and
- Moxifloxacin's ocular penetration exceeded ofloxacin (A2337-38; A1894:21-A1895:18).

Thus, the prior art would have led a POSA to expect topical ophthalmic compositions containing moxifloxacin HCl in a concentration of 0.1-1.0 wt.% to be useful in treating, at the very least, some ophthalmic infections, including conjunctivitis, which the '830 Patent contemplates. A66(2:23-25); A6845 ("highly active against Gram-positive and Gram-negative bacteria"); A6021-23 (same); A6866 ("significantly better than" ciprofloxacin against *Staphylococcus aureus*); A1577:11-A1578:6 (better than ofloxacin against *Pseudomonas aeruginosa*, the cause of conjunctivitis); A1575:10-A1580:5. Moreover, against at least some pathogens, moxifloxacin promised an improved effectiveness or resistance profile

over existing medications. Thus, there was ample motivation to formulate moxifloxacin for topical ophthalmic use.

The District Court found that uncertainties whether moxifloxacin would promote the development of resistant strains of *P. aeruginosa* more than ciprofloxacin in some treatments would discourage a POSA from developing ophthalmic drugs using moxifloxacin. But such uncertainties are irrelevant to the obviousness analysis as a matter of law because Claim 1 does not claim efficacy and resistance improvements of the claimed composition. This Court in *Alcon Research* found obvious a claim to a method of using a prior art compound to treat eye infections and observed:

> Although Alcon argues that Kamei [a prior art reference] would not give a skilled artisan an expectation of success because it does not teach that olopatadine is safe for the human eye, we find this contention to be without merit.… While it is true that Kamei does not expressly disclose that olopatadine would be safe for use in human eyes, neither does the [patent-in-suit].

687 F.3d at 1369. Otherwise stated, uncertainty whether the claimed invention would have unclaimed advantages over prior art is entirely immaterial to the obviousness analysis.

The District Court placed unwarranted emphasis on these uncertainties, merely because the inventors identified the goal of the invention to develop "improved compositions… based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the

development of resistance by those pathogens." A31. But this Court has found legal error when a district court "refus[es] to look at any motivation beyond that articulated by the patent." *Alcon Research*, 687 F.3d at 1368-69. The '942 Patent's and/or Petersen abstract/poster's identification of moxifloxacin as an effective antibiotic against a number of ophthalmic pathogens, in a chemical class from which effective topical ophthalmic medications had previously been formulated, with *in vitro* characteristics superior to some of these medications, provided more than ample motivation to employ moxifloxacin in a topical ophthalmic composition regardless of what may or may not have motivated the inventors.

(b) Alcon's Characterization of Moxifloxacin's Toxicity and Resistance Does Not "Teach Away" from Claim 1

The District Court also applied the wrong legal standard in reaching its conclusion that the prior art taught away from the claimed invention by suggesting that moxifloxacin was eight times less active than ciprofloxacin against *P. aeruginosa*. A34-37. The disclosure of better alternatives and preferred embodiments by prior art does not "teach away" from inferior alternatives and non-preferred embodiments in the art. *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). ("A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination"); *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (a claimed

invention "does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.").

Claim 1 does not recite a pharmaceutical formulation with improved efficacy against *P. aeruginosa*, a "better" resistance profile, or any other alleged "improved" functional feature. Claim 1 simply recites a topical ophthalmic composition comprising "moxifloxacin;" the claim does not even require the "composition" to actually treat any eye infections. Claim 1 does not recite that the composition must somehow perform better than the prior art, for example against any particular pathogen, have a certain resistance profile, have any particular toxicity profile, or have any other property. Even if moxifloxacin were eight times less active than ciprofloxacin against *P. aeruginosa*, moxifloxacin would still be a useful topical ophthalmic pharmaceutical antibiotic composition that a POSA would be motivated to formulate to treat eye infections. There is no "teaching away" because there is nothing in the prior art suggesting that the claimed invention would be unlikely to work for treating eye infections. The prior art certainly did not "clearly discourage" a POSA from using moxifloxacin in a topical ophthalmic composition. *In re Mouttet*, 686 F.3d at 1334.

Similarly, developing a moxifloxacin composition as a new treatment for conjunctivitis, for example, is not discouraged by the art simply because it may be less effective than some prior art compounds at treating other eye infections. *Eli*

Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378 (Fed. Cir. 2006) (indicating that the prior art as a whole must directly teach away from the claimed invention). Indeed, the prior art suggested that moxifloxacin was more active against *P. aeruginosa* than ofloxacin, one of the undisputed state-of-the-art ophthalmic antibiotics at the time.

9. Secondary Considerations Do Not Support the Patentability of Claim 1

"Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008). The evidence at trial concerning secondary considerations lacked the required nexus with Claim 1 and does not support the non-obviousness of Claim 1.

Evidence of commercial success, for example, is probative only if the feature that causes the patentee's product to enjoy commercial success was not "known in the prior art." *Id.* at 1311-12. That is not the case here.

Even if one assumes that Vigamox®'s was a commercial success and that that success is attributable to its effectiveness and not due to advertising or other extraneous factors, Vigamox®'s success is due to features known in the prior art. Moxifloxacin's antibiotic properties were known in the prior art: moxifloxacin, was known to be active against *Staphylococcus aureus* and *Pseudomonas*

aeruginosa (A2335; A2554-57; A2675; A6088-93; A6864-81; A1576:18-A1578:6; A1578:19-A1580:5; A1594:2-13; A1759:16-A1760:16) and to be well-tolerated in humans. A2336-37; A2568; A6845; A1324:19-A1325:21; A1325:9-A1326:7; A1629:3-A1630:18; A1627:2-A1628:20; A2571. Moxifloxacin's antibacterial activity was known to exceed that of ofloxacin (A2335; A2675; A1558:8-14; A1576:18-A1578:6; A1982:4-9; A6845) and ciprofloxacin across a broad range of bacteria. A2335-36; A6866; A6882-83; A6885; A1578:19-A1580:5; A1558:8-22; A1619:24-A1621:25; A1624:21-A1625:13; A2093(1045:23)-A2094(1047:2), A2110(1113:8-A1114:4); A2554-57; A2558-61; A6080-87; A6088-93. Moxifloxacin HCl's solubility in water would have informed a POSA that moxifloxacin HCl could be made into a solution (A1322:21-A1324:18; A1611:22-A1612:21; A6021-23; A6845;A1271:2-19; A1322:13-A1323:10), and that it would penetrate the eye to some degree. A1611:17-A1612:21; A1894:21-A1895:18. These are all the characteristics that led physicians to prescribe Vigamox® and they were all known.

Accordingly, Vigamox®'s commercial success cannot be attributed to something that was unknown or unexpected, but it could well be attributed to the disclosure of the '942 Patent and not any aspect of the '830 Patent. Vigamox®'s commercial success is thus irrelevant to the obviousness analysis. *Muniauction*, 532 F.3d at 1328; *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 460 F. Supp. 2d 659, 666-

67 (D.N.J. 2006); *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("For objective evidence to be accorded substantial weight, *its proponent* must establish a nexus between the evidence and the merits of the claimed invention.") (emphasis added); *Rambus Inc. v. REA*, No. 2012-1634, 2013 WL 5312505, at *7 (Fed. Cir. Sept. 24, 2013) (same).

Similarly, the "unexpected results" of ophthalmic moxifloxacin — eye penetration and effectiveness against *P. aeruginosa* — has no nexus to Claim 1. Moxifloxacin's pharmacokinetic properties are not recited in Claim 1, nor does Claim 1 require effectiveness against *P. aeruginosa*. More importantly, moxifloxacin's efficacy against *P. aeruginosa* was not unexpected. It was known that *P. aeruginosa* was inhibited by high moxifloxacin concentrations and that moxifloxacin has a high aqueous solubility at or near physiological pH, and thus, could be formulated at the claimed range. The Petersen abstract (A6021-23) teaches that moxifloxacin has favorably low MIC values (*supra*) for a wide spectrum of bacteria, and it and the Petersen poster (A6845) suggests it has a high solubility, indicating to a POSA that sufficient moxifloxacin could be supplied to the site of infection to meet or exceed moxifloxacin's MIC value for *Pseudomonas aeruginosa*.

The District Court found a long-felt need based on moxifloxacin's unclaimed effectiveness against ophthalmic pathogens that are not mentioned in

the claims. A36. But Alcon did not show, or even attempt to show, a need at all for what was actually claimed, a topical composition to treat ophthalmic infections (A2423), because then-existing antibacterial agents were known to be effective against such infections. The '942 Patent specifically points out that the compounds disclosed therein can prevent, alleviate, or cure, *inter alia*, eye infections. A2705(54:1-22); A1278:16-A1279:10. As of 1998, fluoroquinolones as a class were known to be effective broad spectrum antibiotics. A1272:23-25; A1268:10-17. By September 1998, two state-of-the-art ophthalmic compositions for the treatment and prevention of ophthalmic infections, identified by Drs. Stroman and Alfonso, were Ciloxan® and Ocuflox® (A1558:8-22; A1667:12-24; A1964:8-23), both of which contained fluoroquinolones as the active pharmaceutical ingredient.

The vague "skepticism" to which Alcon alludes (A2423) is entirely speculative, because Dr. Alfonso could not identify when, where, or, other than in the most general terms, who expressed this alleged "skepticism." A1514:2-A1515:10; A1586:14-A1587:14. Dr. Alfonso's "skepticism" did not extend to whether topical ophthalmic moxifloxacin was an antibacterial agent. A1587:19-A1588:21. And moxifloxacin appeared less susceptible than ciprofloxacin to the development of resistance by at least some bacteria. A1578:19-A1580:5; A1619:19-A1621:25; A1624:21-A1625:13; A2093(1045:23)-A2094(1047:2).

VI. CONCLUSION

The judgment should be reversed. First, the District Court's claim construction derives from a correction that exceeded the District Court's authority as a matter of law and must be vacated. There is no infringement of the claim-in-suit, properly construed. Alternatively, if the District Court properly construed Claim 1, the claim is invalid as obvious.

Date: October 4, 2013

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Christopher A. Harkins, an attorney for Teva Pharmaceuticals USA, Inc., hereby certify that on October 4, 2013, the foregoing **BRIEF OF DEFENDANT-APPELLANT TEVA PHARMACEUTICALS USA, INC.,** was filed electronically with the U.S. Court of Appeal for the Federal Circuit by means of the Court's CM/ECF system and served on the following counsel of record, by means of electronic mail and Pre-Paid U.S. First Class Mail, as well as by the Court's CM/ECF system, which should have sent a Notice of Docket Activity:

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 13,562 words, excluding the parts of the brief exempted by Federal Rule of Appellate procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate procedure 32(a)(6) because this brief has been prepared in proportionally spaced typeface using Microsoft Word in 14-point Times New Roman font.

Dated: : October 4, 2013

/s/ Christopher A. Harkins
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ADDENDUM

Addendum 1

October 19, 2009 Opinion

Alcon, Inc. et al. v. Teva Pharmaceuticals USA, Inc.,
No. 06-234-SLR (D. Del.)

A1-A50

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALCON, INC. and ALCON RESEARCH, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-234-SLR
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

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OPINION

Dated: October 19, 2009
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application (" ANDA")[1] by defendant Teva Pharmaceuticals USA, Inc. ("Teva") to market a generic version of the antibacterial drug VIGAMOX® proprietary to plaintiffs Alcon, Inc., and Alcon Manufacturing, Ltd. (now part of Alcon Research, Ltd.)[2] (collectively, "Alcon"). VIGAMOX® is a topical ophthalmic solution comprised of the active ingredient moxifloxacin hydrochloride, which is protected by, inter alia, U.S. Patent No. 6,716,830 ("the '830 patent"). Teva's ANDA asserts a "Paragraph IV Certification," and seeks approval to market a generic equivalent of VIGAMOX® prior to the expiration of the '830 patent. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Alcon brought this suit against Teva on April 5, 2006, alleging infringement of the '830 patent pursuant to 35 U.S.C. § 271(e)(2)(A).[3] (D.I. 1)

A bench trial commenced February 28, 2008, principally to determine: (1) whether Teva's proposed generic equivalent ("the ANDA product") contains moxifloxacin and so infringes claim 1 of the '830 patent; and (2) whether claim 1 is invalid for anticipation, obviousness or failure to satisfy the best mode, written description, and enablement requirements of 35 U.S.C. § 112. (*Id.* at 4-5) The issues

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[1]No. 78-073.

[2]Alcon Research, Ltd. was substituted for Alcon Manufacturing, Ltd., upon the court's approval of the parties' January 22, 2008 joint stipulation. (D.I. 74)

[3]"(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

were fully briefed post-trial. (D.I. 93; D.I. 107; D.I. 108; D.I. 111; D.I. 112; D.I. 115)

The court has jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT

A. Parties

Plaintiff Alcon, Inc. is a Swiss corporation with its principal place of business in Hünenberg, Switzerland. (D.I. 79, ex. 1 at ¶ 3) It is the assignee and owner of the '830 patent. (*Id.* at ¶ 23) Plaintiff Alcon Research, Ltd., is a Delaware corporation with its principal place of business in Fort Worth, Texas. (*Id.* at ¶ 4) It is the exclusive licensee of the '830 patent. (*Id.* at ¶ 24)

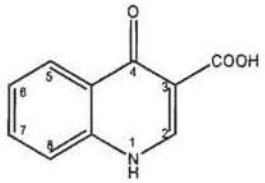
Alcon sells a topical ophthalmic pharmaceutical solution under the tradename VIGAMOX®. (*Id.* at ¶ 26) Alcon is the holder of a Food and Drug Administration ("FDA")-approved New Drug Application ("NDA") for VIGAMOX® and has listed the '830 patent, among others, in the FDA's Orange Book for VIGAMOX®. (*Id.* at ¶ 28)

Teva is a wholly-owned subsidiary of Teva Pharmaceuticals Industries, Ltd. (*Id.* at ¶ 59) Teva is a Delaware corporation with its principal place of business in Pennsylvania. (*Id.* at ¶ 5) Teva engages primarily in the manufacturing and marketing of generic drugs.

B. Moxifloxacin

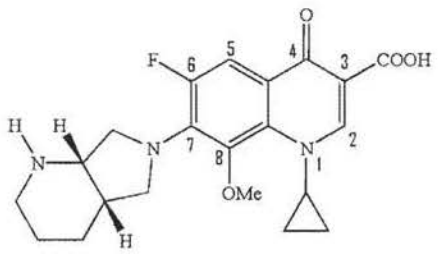
Quinolone carboxylic acids, or "quinolones," are a class of antibacterial

compounds that share a common core chemical structure, depicted as follows:



(*See* PTX 2003) The numbers along the diagram of the molecule represent positions at which functional groups may attach. (D.I. 100 at 54-55) The "COOH" at the 3-position represents a carboxylic acid. (*Id.* at 55) A carboxylic acid at the 3-position, along with a nitrogen-containing carbon ring and a double-bonded oxygen, are fundamental and common aspects of all quinolone antibiotics. (*Id.*)

Prior to July 28, 1998, the World Health Organization ("WHO") proposed the international nonproprietary name ("INN") "moxifloxacin"[4] for the quinolone depicted below:



(D.I. 100 at 60; PTX 139 at 187) Moxifloxacin, like other quinolones, possesses a carboxylic acid at the 3-position, double-bonded oxygen and a nitrogen-containing fused carbon ring. (PTX 3 at col. 98, ll. 55-65) The bicyclic amine attached at the 7-

[4]WHO used the suffix "-oxacin" as the stem name for quinolones. (D.I. 100 at 62; PTX 152 at 21)

position, a feature that distinguishes moxifloxacin from other quinolones, contains two chiral carbons. Because of these two chiral carbons, there are four possible stereochemical arrangements[5] for this molecule. (D.I. 79, ex. 1 at ¶ 68) Two of these arrangements are cis isomers, and the remaining two are trans isomers.[6] (*Id.*) The two cis compounds (denoted as "S,S" and "R,R") act as mirror images of each other, thus constituting a pair of enantiomers, while the two trans compounds ("S,R" and "R,S") constitute a second pair of enantiomers. (*Id.*) Often, enantiomers will significantly differ from each other in terms of pharmocology.[7]

Moxifloxacin has an "S,S" configuration at the chiral carbons in the 7-position bicyclic amine. (*Id.* at ¶ 70) The bolded carbon-hydrogen bonds in the figure above depict this configuration, indicating that the bonds extend upward from the rest of the molecule, which exists in the plane of the page. By contrast, the carbon-hydrogen bonds at the chiral carbons of the corresponding compound with the "R,R" configuration (the "R,R enantiomer") would extend downward beyond the plane of the paper. (*Id.*) These graphical conventions are unnecessary for named structures with known stereochemistry; the name imparts such information. (D.I. 100 at 85)

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[5]While several compounds may have the same chemical formulas and connectivity, their orientation in 3-dimensional space may differ. These alternate arrangements are known as sterioisomers.

[6]"Cis" indicates here that the hydrogen atoms on the carbons shared by the two rings are on the same side of the molecule, while "trans" indicates that the hydrogen atoms on the carbons shared by the two rings are on opposite sides of the molecule.

[7]Thus making one enantiomer much more attractive to pharmaceutical companies. Indeed, there are many blockbuster single-enantiomer drugs. *See* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 Stan. Tech. L. Rev. 2, 7 (2007).

Bayer AG ("Bayer") began developing moxifloxacin under the guise of BAY 12-8039, the company's designation of moxifloxacin hydrochloride ("moxifloxacin HCl"). (*Id.* at 135) Bayer is the holder of U.S. Patent No. 5,607,942 (the '942 patent),[8] which claims the compound moxifloxacin[9] and its sterioisomers. (PTX 3 at col. 98, l. 51- col. 99, l. 2) BAY 12-8039 became the subject of several studies with respect to its efficacy in combating gram-positive and gram-negative bacteria. (PTX 1124; PTX 1125; PTX 137) The specification of the '942 patent itself generally describes the efficacy of the numerous compounds disclosed as "exhibit[ing] a broad antibacterial spectrum against Gram-negative and Gram-positive bacteria . . . ." (PTX 3 at col. 53, ll. 22-27)

Satisfied with the pharmaceutical potential of BAY 12-8039, Bayer filed a NDA under the tradename AVELOX® with the FDA. This application was directed towards a 400 mg tablet form of moxifloxacin. (D.I. 105 at 1052) As of 1996, BAY 12-8039 had entered into Phase II of the NDA process. (PTX 1098) However, only Phase I[10] toxicity

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[8]The '942 patent issued on March 4, 1997.

[9]Because WHO had not yet determined the INN "moxifloxacin," the '942 patent identifies the compound both by structure and systematic (IUPAC) name: 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo [4.3.0]non-8-yl] -6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3- quinolinecarboxylic acid. (PTX 3 at col. 98, ll. 52-65)

[10]Phase I of the NDA process focuses upon testing the proposed drug for acute toxicity in a small, healthy audience of volunteers. (D.I. 101 at 345) Generally considered a low hurdle to clear, toxicity may not appear in Phase I at all. (*Id.*) Indeed, toxicity may remain hidden until Phase II testing, which focuses upon drug efficacy and determining the clinically appropriate dose in a larger, less robust audience, or even after the drug is approved for distribution. (*Id.*) Thus, the successful completion of Phase I trials is often poorly predictive of the existence of toxicity.

The general caveat with respect to Phase I data applies with full force to quinolones. (D.I. 103 at 908) Indeed, many quinolones that successfully completed Phase I subsequently failed to pass muster in Phase II, Phase III or the post-approval stage when unacceptable toxicities were detected. (*Id.* at 908; PTX 2025)

data for moxifloxacin was available as of September 1998. (D.I. 103 at 906-07) The FDA approved Bayer's NDA for AVELOX® on December 10, 1999. (D.I. 104 at 1051)

C. The Invention and the '830 Patent

Dr. David Stroman is a clinical microbiologist employed by Alcon who is also involved in the selection and screening of potential ophthalmic and otic compositions. (D.I. 102 at 565, 570-571) At trial, Dr. Stroman testified that, in 1998, the focus in the art was upon the need to develop efficacious treatments for intraocular infections caused by *Staphylococcus aureus*, a gram-positive bacteria, and *Pseudomonas aeruginosa*, a gram-negative bacteria. (*Id.* at 566) Alcon, specifically, sought a compound that could both treat infections caused by these pathogens and act as a prophylactic measure to prevent infection at the time of surgery. (*Id.* at 569)

Both pathogens, which cause sight-threatening infections inside the eye, displayed emerging resistance[11] to quinolone treatment. (*Id.*) However, resistance to *Pseudomonas aeruginosa* caused investigators greater concern, because it was considered the most threatening ocular pathogen. (*Id.*) Maintaining activity against *Pseudomonas aeruginosa* while enhancing activity against *Staphylococcus aureus* became objectives of the search. (D.I. 101 at 402) In 1998, ciprofloxacin,[12] the then-

[11]If a bacterial strain becomes resistant to one quinolone, it becomes resistant to all other quinolones. (D.I. 101 at 398-99) This phenomenon is known as a "class effect." Such resistance is generated when a weak drug fails to completely eradicate the bacterium. (D.I. 103 at 877) Scientists investigating quinolones would only consider a compound viable if characterized by a certain minimum activity against the target pathogens. (D.I. 103 at 856)

[12]Marketed by Alcon under the tradename CILOXAN®, ciprofloxacin had "tremendous activity and potency against . . . *Pseudomonas aeruginosa.*" (*Id.*) It displayed less than desirable activity against *Staphylococcus aureus*. (*Id.* at 857)

state-of-the-art treatment for ophthalmic infections, served as the standard for microbiological activity against ocular pathogens. (D.I. 102 at 568; D.I. 103 at 856)

Dr. Stroman further testified that, by contrast, the medical community had no need for new treatments solely for surface infections, such as conjunctivitis.[13] (D.I. 101 at 389-91; D.I. 102 at 566-67; D.I. 103 at 844-45) Such infections held little chance of causing serious damage, were adequately controlled by existing products and often resolved without treatment. (*Id.*)

These parameters guided Dr. Stroman's analysis of roughly one hundred compounds between 1990 (when he joined Alcon) and 1998. (D.I. 102 at 570) He encountered *in vitro* data for BAY 12-8039 on a Bayer poster at the 1997 ICAAC[14] conference in Toronto. (*Id.* at 571; PTX 1098) This data indicated that, while BAY 12-8039 was more active than ciprofloxacin against *Staphylococcus aureus*, it was eight times less active against *Pseudomonas aeruginosa*. (*Id.*) Dr. Stroman left the conference with a list of 10-15 compounds that he had interest in obtaining for further analysis. (*Id.* at 572) Despite his concerns about the *in vitro* activity data, Dr. Stroman requested from Bayer a sample of BAY 12-8039. (D.I. 103 at 645; PTX 1065)

Dr. Stroman received a 10 gram sample of BAY 12-8039 on January 4, 1999. (*Id.* at 585; PTX 89) A multi-departmental investigation confirmed Bayer's *in vitro* data

[13]Conjunctivitis, commonly referred to as "pink eye", is a surface infection of the conjunctival membrane. (D.I. 100 at 174;D.I. 101 at 389-90)

[14]The Interscience Conference on Antimicrobial Agents and Chemotherapy.

for BAY 12-8039. (D.I. 102 at 591) However, an *in vivo* test[15] of the sample painted a different picture. (D.I. 102 at 594-95) When applied as a topical ophthalmic composition, moxifloxacin was shown to treat and prevent intraocular *Pseudomonas aeruginosa* infections, including resistant strains, as effectively as ciprofloxacin, without resistance developing rapidly. (*Id.*) Furthermore, in a separate test, moxifloxacin displayed an ocular penetration[16] greater than two times that of ofloxacin,[17] the best ocular-penetrating quinolone product available. (D.I. 102 at 597-98)

On September 30, 1998, months before Dr. Stroman even received the sample of BAY 12-8039, Alcon filed U.S. Provisional Patent Application Nos. 60/102,506 ("the '506 application") and 60/102,504 ("the '504 application") with the United States Patent & Trademark Office ("PTO"). (D.I. 102 at 573) Both applications were directed towards ophthalmic compositions containing moxifloxacin. (*Id.*) This early filing was motivated in part to avoid any future proprietary struggle between Alcon and Bayer should any novel developments result from Alcon's analysis of BAY 12-8039. (*Id.* at 574) After determining that moxifloxacin met all of Dr. Stroman's search parameters while providing enhanced ocular delivery, Alcon proceeded with its prosecution of the '506 and '504 applications.

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[15]The *in vitro* data resulted from a test tube analysis of the microbiological activity of moxifloxacin. (D.I. 103 at 899) The *in vivo* test, by contrast, involved injection of the bacteria directly into the eye of a rabbit, followed by subsequent application of a moxifloxacin solution to the ocular surface. (D.I. 102 at 593) Scientists then harvested the cornea and analyzed the microbiological activity. (*Id.*)

[16]Ocular penetration refers to the desirable ability of the compound to diffuse through the protective layers of the eye.

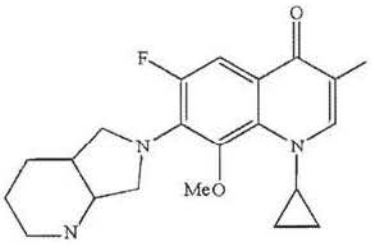
[17]Manufactured by Allergan under the tradename OCUFLOX®.

The '830 patent, entitled "Ophthalmic Antibiotic Compositions Containing Moxifloxacin," issued on April 6, 2004. (D.I. 79, ex. 1 at ¶ 15) The '830 patent ultimately matured from U.S. Patent Application No. 10/200,868 ("the '868 application"), which was filed with the PTO on July 22, 2002. (*Id.* at ¶ 16) The '868 application claims priority, through U.S. Patent Application No. 09/646,797 ("the '797 application") which was the National Stage of International Application No. PCT/US99/22622, to the '506 and the '504 applications. (*Id.* at ¶ 17) The parties agree that, for purposes of this action, the effective filing date of the '830 patent is September 30, 1998. (*Id.* at ¶ 18)

The '830 patent is directed towards topical ophthalmic antibiotic compositions. (PTX 5 at col. 1, ll. 13-21) Claim 1, the sole independent claim and the only asserted claim in this litigation, provides:

> A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt % and pharmaceutically acceptable vehicle therefor.

(*Id.* at col. 7, ll. 29-32) The specification of the '830 patent discloses the following structure for moxifloxacin:



(*Id.* at col. 3, ll. 36-48) Notably absent from this representation of moxifloxacin is the 3-position carboxylic acid. (*Id.*) Likewise, the '830 patent omits any graphical depiction of moxifloxacin's stereochemistry. (*Id.*) However, the '830 patent provides that "[f]urther details regarding the structure, preparation, and physical properties of [m]oxifloxacin . . . are provided in U.S. Pat. No. 5,607,942." (*Id.* at col. 3, ll. 49-51)

Neither the '830 patent nor any of the applications to which it claims priority disclose moxifloxacin HCl as an embodiment of the invention. Moxifloxacin HCl, the active ingredient in both VIGAMOX® and defendant's ANDA product, is the hydrochloride salt of pure (betaine) moxifloxacin. (*Id.* at ¶ 69) When compared to moxifloxacin betaine, moxifloxacin HCl displays an enhanced solubility. (D.I. 100 at 143) Dr. Ted Taylor, Professor Emeritus of Chemistry at Princeton University, testified for plaintiffs that moxifloxacin HCl and moxifloxacin betaine will both dissolve into a solution over the claimed concentration range of the '840 patent. (*Id.* at 143) Although a solution based on moxifloxacin HCl will result in a different pH than a solution based on moxifloxacin betaine, once either form is dissolved into a solution, there is no difference[18] in microbiological activity, efficacy or toxicity. (*Id.* at 95; D.I. 104 at 1032, 1037)

At the time that Alcon filed the '506 and '504 applications, the only form of moxifloxacin known to Dr. Stroman, one of three inventors listed in the '830 patent, was that of BAY 12-8039 - moxifloxacin HCl. However, much of the correspondence between Dr. Stroman and others regarding the sample of BAY 12-8039 refer to the

[18]Moxifloxacin HCl, an acid addition salt, will dissociate into moxifloxacin upon addition to a solution.

compound, if other than by Bayer's internal designation, simply as moxifloxacin. (PTX 402 at 1; PTX 399; PTX 89) At trial, Dr. Stroman disavowed any particular preference for the salt or betaine form of moxifloxacin, testifying that "I can't say that I ever even understood there was [a] salt form because I was focused on the active." (D.I. 102 at 577-578)

D. The ANDA Product

On or about December 25, 2005, defendant filed its ANDA.[19] (D.I. 79, ex. 1 at ¶ 30) The ANDA lists plaintiffs' VIGAMOX® as the reference drug and seeks approval for identical conditions of use. (PTX 11 at 19) Both the ANDA product and VIGAMOX® contain as the active ingredient moxifloxacin HCl (0.5 wt %). (*Id.*)

E. Asserted Prior Art

The asserted prior art relating to the '830 patent includes: (1) prior art relating to ophthalmic antibiotic compositions; and (2) prior art relating to moxifloxacin, particularly moxifloxacin HCl (i.e. BAY 12-8039). (D.I. 107 at 15)

1. Prior art relating to ophthalmic antibiotic compositions

The two state-of-the-art ophthalmic compositions in September 1998 for the treatment and prevention of ophthalmic infections were CILOXAN® and OCUFLOX® (D.I. 101 at 459; D.I. 102 at 568), both of which contained quinolones as the active pharmaceutical ingredient. (D.I. 100 at 172, 194) The prior art also included Alcon's U.S. Patent No. 5,149,693 ("the '693 patent"), which discloses ophthalmic antibiotic compositions containing tobramycin. (DTX 78; D.I. 100 at 208, 213)

[19]The ANDA is entitled "Moxifloxacin Hydrochloride Ophthalmic Solution, 0.5% base." (D.I. 79, ex. 1 at ¶ 30)

a. CILOXAN® ophthalmic solution and ointment

CILOXAN® ophthalmic solution was approved by the FDA on December 31, 1990. (DTX 141; D.I. 100 at 195) CILOXAN® ophthalmic solution contains 0.35 wt % of ciprofloxacin hydrochloride as the active ingredient. (DTX 144; D.I. 100 at 194)

As of 1998, CILOXAN® was also marketed by Alcon as an ophthalmic ointment. (PTX 1063; D.I. 100 at 202) CILOXAN® ointment was approved by the FDA on March 30, 1998. (PTX 146; D.I. 100 at 203) It contains 0.3 wt % of ciprofloxacin hydrochloride as the active ingredient. (PTX 1063; D.I. 100 at 202-03)

b. OCUFLOX® ophthalmic solution

OCUFLOX® was marketed by Allergan, Inc., as of 1995. (DTX 159; D.I. 101 at 220) It contains 0.3 wt % of ofloxacin as its active ingredient. (DTX 159; D.I. 101 at 220-21)

c. TOBRADEX® ophthalmic suspension

TOBRADEX® ophthalmic suspension is an antibiotic composition that contains tobramycin, which is an aminoglycoside antibiotic. (DTX 145; D.I. 100 at 207, 208) Alcon manufactures TOBRADEX® ophthalmic suspension and has had it on the market since 1996. (DTX 145; D.I. 100 at 208) The active ingredients in TOBRADEX® ophthalmic suspension are tobramycin (0.3 wt %) and dexamethasone (0.1 wt %), the latter an anti-inflammatory. (DTX 145; D.I. 101 at 208)

d. The '693 patent

The '693 patent is titled "Combination of Tobramycin and Fluorometholone for Topical Ophthalmic Use." (DTX 78) It issued on September 22, 1992, and is assigned to Alcon. (*Id.*; D.I. 100 at 213) Example II of the '693 patent is

Fluorometholone acetate, USP	0.1% + 2% excess	1 mg + 2% excess
Tobramycin; Micronized, USP	0.3% + 7% excess	3 mg + 7% excess
Chlorobutanol, Anhydrous, NF	0.5% + 25% excess	5 mg + 15% excess
Mineral Oil, USP	5%	50 mg
White Petroleum, USP	QS 100%	QS 1 g

(DTX 78, Col. 2, ll. 60-65)

2. Prior art relating to moxifloxacin

a. The '942 patent

The application leading to the '942 patent was filed on March 20, 1995 as a divisional application (in a chain of divisionals) claiming priority to U.S. Patent No. 4,990,517, and issued on March 4, 1997. The specification of the '942 patent discloses numerous quinolone compounds. (PTX 5) Drawing upon the antibacterial aspect of quinolones as a class, the '942 patent details a laundry list of maladies, including "eye infections," which may be treated by the disclosed compounds. (*Id.* at col. 54, ll. 7-22) The claims of the '942 patent are directed to a specific quinolone and its four stereoisomers, one of which is moxifloxacin. (*Id.* at col. 98, l. 51-col. 99, l. 17)

b. Pre-1998 publications

Publications as of 1998 indicated that moxifloxacin displayed a more desirable resistance profile than ciprofloxacin against certain bacteria, including *Staphylococcus aureus*. (PTX 1124) However, the bacteria studied were either not identified to be ocular pathogens or, in the case of *Staphylococcus aureus*, not identified as originating from an ocular source. (*Id.*; D.I. 102 at 520-22)

Furthermore, several physical properties of moxifloxacin had been reported as of this time. Solubility data indicated that moxifloxacin could be made into a solution. (D.I. 102 at 512-13) The pharmacokinetics of moxifloxacin showed that the compound "could

effectively penetrate[ ] extravascular tissue,[20] including lung tissue." (PTX 223 at 2060) Likewise, moxifloxacin was known to penetrate the protective cerebrospinal fluid barrier of the brain. (DTX 191; D.1. 102 at 517-18)

III. CONCLUSIONS OF LAW

A. Infringement

"'It shall be an act of infringement to submit' an ANDA to the FDA seeking approval 'to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.'" *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, 2009 WL 1838352 *7 (D. Del. Apr. 3, 2009) (quoting 35 U.S.C. § 271(e)(2)). To determine whether a composition identified in an ANDA is a composition claimed in a patent, the court conducts the familiar two-step infringement inquiry: first, the court construes the patent claims; second, it compares the construed claims to the accused product to determine whether every claim limitation is found in the accused product. *See, e.g., Roche Palo Alto LLC v. Apotex, Inc.*, 531 F.3d 1372, 1377 (Fed. Cir. 2008) (condoning use of the two-step infringement inquiry in the ANDA context). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

In this case, the two-step infringement inquiry is, to a degree, simplified. With one exception, the parties agree that defendant's ANDA product contains every limitation of

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[20]While "extravascular tissue" technically includes the eye, the parties dispute whether this statement would have been interpreted as indicia of ocular penetration. (D.I. 102 at 515; D.I. 103 at 952)

the '830 patent. (*See* D.I. 79, ex. 1 at ¶¶ 45, 58, 77) That one exception, or point of dispute, is whether the ANDA product contains "moxifloxacin" as it is used in claim 1, and the parties agree that the court's construction of "moxifloxacin" is dispositive of plaintiffs' infringement claim. (*See id.*) To wit, if the court construes the "moxifloxacin" disclosed in claim 1 in accordance with the general understanding of that term in the scientific community, then the ANDA product infringes, because there is no dispute that the ANDA product contains moxifloxacin. (PTX 11; D.I. 79, ex. 1 at ¶¶ 45, 58, 77) Conversely, if the court construes the "moxifloxacin" disclosed in claim 1 as being a compound other than moxifloxacin, the ANDA product does not contain all the limitations of the '830 patent and so does not infringe. The court focuses, then, on construing "moxifloxacin."

1. Claim construction generally

As a general matter, the court construes the words of a claim according to "their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). A claim term's "ordinary and customary meaning" "is the meaning that the term would have to a person of ordinary skill in the art in the question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* "[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* Where "the meaning of a claim term as understood by persons of skill in the art is . . . not immediately apparent," the court turns to publicly-available sources to ascertain the meaning, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic

evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quotation marks omitted).

2. Person of ordinary skill in the art

To determine the person of ordinary skill in the art, the court may consider various factors, including: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983). Courts use these factors as a guide, and the weight or significance the court ascribes to these or similar factors will depend on the case. *See id.* at 696-697; *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007).

Applying the factors in this case, the court concludes that the ordinary person of skill in the art would be a person with a Ph.D in microbiology or an M.D. with training in ophthalmology, that is, a person with knowledge of chemistry, ophthalmic pathogens, and antibiotic compounds sufficient to appreciate the relative merit of various antibiotic compositions in treating and preventing ophthalmic infections. The inventors responsible for claim 1, all of whom possess Ph.Ds in microbiology, would be typical of that person.[21] Further, the '830 patent was addressed to the problem of finding an

[21]Defendant seeks to render immaterial the formal education of the inventors because of the lack of microbiological tests performed during the development of the subject matter of the '830 patent. Such a theory wrongly suggests that the skill set of microbiologists is limited solely to physical testing, and is inconsistent with the myriad skills employed by Dr. Stroman, a microbiologist, in his assessment of the needs in the field of treating and preventing ophthalmic infections and in his selection of compounds to meet those needs.

antibiotic composition that could more effectively treat and prevent ophthalmic infections while deterring key ophthalmic pathogens from developing resistance; the person of ordinary skill in the art described above would understand the problem and whether a proffered treatment solved it. Specifically, the person of ordinary skill in the art described above would be able to analyze both the effectiveness of the antibiotic composition against the key pathogens and the composition's toxicity to humans, which ultimately determines the composition's suitability as a treatment.

Teva argues that the person of ordinary skill in the art is someone with experience solely in formulation. (D.I. 107 at 23) This argument has some intuitive appeal, since the aim of the '830 patent is, ultimately, to formulate a composition for opthalmic use. However, a formulator without knowledge of microbiology or ophthalmology would not be able to appreciate the inventive aspect of the patent, which is the selection of moxifloxacin for an ophthalmic composition, instead of some other antibiotic compound. Indeed, without these tools a formulator would be ill-equipped to assess the efficacy and resistance profile of a given treatment. *Cf. DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1362 (Fed. Cir. 2006) (ordinary person of skill in the art must be "concerned" with the problems the patent seeks to address). Moreover, it is clear from the specification's sparse guidance with respect to formulation that the patent was not directed towards resolving issues in this field. Accordingly, while the person of ordinary skill in the art might have some experience with formulation, he or she will not be a formulator, but rather someone with advanced training in microbiology or ophthalmology.

3. Meaning of "moxifloxacin" to person of ordinary skill in the art

The court first addresses Teva's redefinition argument. Teva maintains that Alcon has redefined the "moxifloxacin" of claim 1 of the '830 patent to represent the compound depicted in the specification. Indeed, it is well settled that "inventor's lexicography governs" when the specification reveals a special definition for a claim term that "differs from the meaning it would otherwise possess." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). Teva contends that, because the specification of the '830 patent provides an alternate meaning for the claim term "moxifloxacin" in the form of the depiction of a structurally different compound, the ordinary meaning of moxifloxacin has been displaced. (D.I. 108 at 2) Teva marshals support for its proffered meaning by pointing to a specific reference in the specification to a "new class of antibiotics." (PTX 5 at col. 1, ll. 18-19) Quinolones, Teva argues, were not a new class of antibiotics; therefore, the subject matter of the '830 patent must be directed to a different family of compounds.[22] (D.I. 108 at 4)

The court rejects Teva's proposed construction. In order for a patentee to act as his own lexicographer, any redefinition must "appear with reasonable clarity,

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[22]Teva seeks, in the alternative, to distinguish its generic moxifloxacin product on grounds of stereochemistry. (D.I. 108 at 1) Specifically, Teva points to the absence of graphical indicia of stereochemistry in the '830 patent, and asserts that Alcon has claimed a racemic mixture, or a 50/50 mixture of enantiomers, instead of just the S,S enantiomer, which is the active ingredient in both VIGAMOX® and Teva's generic product.

This is unpersuasive. That a molecule has a known stereochemistry does not require the graphical depiction of such. As discussed previously, the names of certain compounds will themselves convey such information. Moxifloxacin is one of these names. Furthermore, even the failure to graphically indicate the stereochemistry of a molecule without known stereochemistry does not mandate an interpretation that it is a racemic mixture. Indeed, scientists have indicated racemic mixtures by including, next to the structures, conventions such as RAC, (racemic), DL or RS. (D.I. 100 at 87)

deliberateness, and precision before it can affect the claim." *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1355 (Fed. Cir. 2003) (internal quotation marks omitted); *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). The record before the court is replete with instances in which Teva's proposed construction is at odds with the specification of the '830 patent so as to cause an absence of the requisite clarity, deliberateness and precision. *See id.*

First, it is clear that the "new class of antibiotics" refers to the class of compounds depicted in the specification by formula (I).[23] Formula (I) depicts the general structure of quinolone compounds. (PTX 5 at col. 2, ll. 50-60) The specification further provides that "moxifloxacin is [the] most preferred" within the formula's class of compounds. (PTX 5 at col. 3, l. 36) Here, Teva's construction is precluded because formula (I) would not encompass a compound containing a 3-position methyl group[24] or, in the alternative, lacking a 3-position carboxylic acid.[25]

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[23]"The compositions and methods of the invention are based on the use of a new class of antibiotics." (PTX 5, at col. 1, ll. 18-19); "The antibiotics used in the compositions and methods of the present invention have the following formula: (I)." (*Id.* at col. 2, ll. 48-50); "Compositions of the present invention will contain one or more compounds of formula (I)." (*Id.* at col. 5, ll. 55-58)

[24]Teva argues that the line at the 3-position of "moxifloxacin" in the '830 patent represents a methyl group. (D.I. 108 at 13) While one convention for drawing organic molecules includes the use of lines to indicate methyl groups, using "Me" to indicate such groups is another popular practice. (D.I. 100 at 70) Generally, conventions are consistent throughout the structure. (*Id.* at 70-71) Teva has declined to comment on the presence of both conventions in the '830 patent's depiction of moxifloxacin. This, of course, militates toward the finding that a typographical error in the form of an omission, and not a methyl group, exists at the 3-position of "moxifloxacin" in the '830 patent.

[25]The 3-position may also exist as an ester, which is a pro-drug form of the active carboxylic fuctionality. (PTX 5 at col. 2, l. 48 - col. 3, l. 35)

A conflict is also readily apparent between the portion of the specification immediately below the structure and the alleged alternative meaning of moxifloxacin. The '830 patent explains, "[f]urther details regarding the structure, preparation, and physical properties of [m]oxifloxacin and other compounds of formula (I) are provided in U.S. Pat. No. 5,607,942." (*Id.* at col. 3, ll. 49-50) As stated, *supra*, the '942 patent is directed to the disclosure of numerous quinolone compounds and specifically claims the structure which would later receive the INN moxifloxacin. The '942 patent offers absolutely no guidance regarding a structure with a 3-position methyl group. Thus, the incorporation by reference to the '942 patent buttresses the conclusion that the inventors of the '830 patent did not define a novel compound that did not belong to the quinolone class.

The specification, when viewed as a whole, does not clearly, deliberately or precisely indicate that the inventors have acted upon their lexicographic license to change the meaning of moxifloxacin. *See Abbott Labs.*, 334 F.3d at 1355. The court, therefore, finds that the inventors of the '830 patent did not redefine moxifloxacin; rather, a typographical error exists at the 3-position of the structure.

This conclusion is supported by an examination of the prosecution history and all relevant extrinsic evidence. *See Phillips*, 415 F.3d at 1314. The file history of the '830 patent reveals a mutual understanding between the PTO and the inventors that moxifloxacin was a compound well known in the art. (PTX 6 at BA001-002828) Indeed, the examiner initially rejected the claims of the '797 application as anticipated by the '942 patent. (*Id.*) In traversing the rejection, Alcon explained that, while moxifloxacin was disclosed in the '942 patent, ophthalmic compositions containing moxifloxacin were

not. (*Id.* at 2839) This comports with the testimony of Dr. Stroman, who explained that the patentees were claiming a novel ophthalmic composition containing the previously known moxifloxacin and not "the use of a brand new compound in an ophthalmic composition." (D.I. 102 at 618-19)

The international naming conventions of the WHO would likewise assist in conveying the ordinary and accustomed meaning of moxifloxacin. A person of ordinary skill in the art would understand from the nomenclature alone, specifically the suffix "-oxacin," that moxifloxacin belonged to the class of quinolone antibacterial compounds. (D.I. 100 at 61; *id.* at 77) A person of ordinary skill would also understand that, because the WHO had already proposed the name "moxifloxacin" as of the priority date, moxifloxacin designated a specific structure and stereochemistry. (*Id.* at 120-21)

In view of the specification, the claims, the prosecution history and all relevant extrinsic evidence, the court concludes that a person of ordinary skill in the art would understand "moxifloxacin," as used in claim 1 of the '830 patent, to indicate the quinolone compound of the same name, whose structure, stereochemistry and other properties were well known as of the priority date.

4. Existence of infringement

Having construed "moxifloxacin" according to its ordinary and accustomed meaning, the court finds that the generic moxifloxacin product described in Teva's ANDA infringes claim 1 of the '830 patent.

B. Validity

A patent is presumed valid and the burden of proving invalidity, whether under 35 U.S.C. § 112 or otherwise, rests with the challenger. *See* 35 U.S.C. § 282. In order to

overcome this presumption, the party challenging validity bears the burden of proving, by clear and convincing evidence, that the invention fails to meet the requirements of patentability. *See Hewlett-Packard Co. v. Bausch & Lomb*, 909 F.2d 1464, 1467 (Fed. Cir. 1990). Clear and convincing evidence is evidence that "could place in the ultimate factfinder an abiding conviction that the truth of [the] factual contentions [is] 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984).

1. Anticipation

a. Legal standard

Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or to avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Id.* (internal citations omitted). The prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be anticipating. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

A prior art reference also may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *See id.* That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* The Federal Circuit also has observed that "[i]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. V. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *Id.* at 1377.

An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *See Key Pharms. v. Hercon Labs Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *See id.* A finding of anticipation will invalidate the patent. *See Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 147 F.3d 1374, 1378 (Fed. Cir. 1998).

b. Discussion

Teva argues that the '830 patent is invalid as anticipated by the '942 patent. Specifically, Teva contends that the '942 patent discloses each limitation of claim 1 of the '830 patent. The parties agree that the '942 patent discloses a "topical ophthalmic pharmaceutical composition." (D.I. 107 at 38; D.I. 112 at 42) In light of the court's construction of "moxifloxacin" *supra*, the court finds that the '942 patent also discloses

"moxifloxacin or a pharmaceutically useful hydrate or salt thereof." In order for Teva to succeed, it must show that the '942 patent discloses the concentration range of 0.1 to 1 wt% and a "pharmaceutically acceptable vehicle."

With respect to the concentration range, the '942 patent states that "[t]he therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5, preferably about 0.5 to 95% by weight of the total mixture." (PTX 3 at col. 56, ll. 7-10) Teva argues that the disclosed ranges of the '942 patent encompass the 0.1 to 1.0 wt% range claimed in the '830 patent. Teva also alleges the existence of an "inherent range" of 0.1 to 0.5 wt%, resulting from the difference between the low ends of the two explicitly disclosed ranges. Teva asserts that both the explicit and inherent ranges place a person of ordinary skill in the art in possession of the concentration range limitation of claim 1.[26]

A small genus may disclose each species encompassed by that genus, so as to anticipate later claims to the species. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). However, it does not follow that the prior art disclosure of a larger genus necessarily results in the disclosure of every species contained within. *See id.* In *Atofina*, the Court found that the prior art's disclosure of the temperature ranges 150 to 350C and 100 to 500C did not disclose the claimed range of 330 to 450C.

[26]Teva also offers evidence regarding the composition of CILOXAN® and OCUFLOX® in order to demonstrate the existence of ophthalmic formulations within the claimed concentration range of the '830 patent. Teva essentially argues that this information, combined with the disclosure of the '942 patent, anticipates claim 1 of the '830 patent. Anticipation, unlike obviousness under § 103, requires a single reference to disclose each and every claim limitation. *See Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Thus, the court will confine its analysis under § 102 to the '942 patent, which is the only asserted anticipatory prior art.

See id. at 1000 (explaining that "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim."). The range disparity in *Atofina* is magnified in the case at bar, the claimed range of the '830 patent a mere fraction of the range disclosed by the '942 patent. The court finds that this "considerable difference" renders the expansive range disclosed by the '942 patent non-anticipatory.

Teva also points to an "inherent range" of 0.1 to 0.5 wt% disclosed in the '942 patent. Certainly, the prior art disclosure of a species will anticipate a genus claim encompassing that species. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985). Thus, it is axiomatic that a concentration range of 0.1 to 0.5 wt% would anticipate a later claim to a range of 0.1 to 1.0 wt%. The court, however, finds that the '942 patent discloses no such range. Teva has constructed this range in an impermissible attempt to attach significance to the end points of the two explicitly disclosed ranges in the '942 patent. *Atofina*, 441 F.3d at 1000. The disclosure in the '942 patent "is only that of a range, not a specific [concentration] in that range, and the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." *Id.*

The '942 patent also fails to describe the "pharmaceutically acceptable vehicle" of claim 1. Teva argues that the list of "customary excipients" provided by the '942 patent discloses this limitation. (PTX 3 at col. 55, ll. 50-59) Within this list, Teva focuses upon the disclosure of water, which forms a substantial part of ophthalmic solutions. (D.I. 100 at 193) However, ophthalmic compositions require a delicate balance of constituents to

qualify as pharmaceutically acceptable. Indeed, several components may be required to obtain the necessary levels of sterility, stability and toxicity, which water alone cannot provide.[27] (D.I. 101 at 276-277;D.I. 102 at 695-696) Furthermore, the excipients used in ophthalmic applications will differ from those applied to different areas of the body. The '942 patent provides a list of excipients, but lacks guidance as to which excipients are suitable to create a "pharmaceutically acceptable vehicle" for an ophthalmic composition. Therefore, the court finds that the '942 patent fails to disclose a "pharmaceutically suitable vehicle."

Teva has failed to demonstrate, by clear and convincing evidence, that the '942 patent discloses either the concentration range or the "pharmaceutically suitable vehicle" of the '830 patent. In view of the foregoing, the court finds that claim 1 of the '830 patent is not invalid for anticipation.

2. Obviousness

a. Legal standard

"A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

[27]This is made especially evident by the examples of solutions, suspensions and ointments provided in the '830 patent. While water comprises a relatively large percentage by weight in the solution and suspension examples, several other components are necessary to achieve the proper vehicle. (PTX 5 at col. 6, l. 34 - col. 7, l. 23)

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 407 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 419. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show, by clear and convincing evidence, that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 421-22. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 422. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.*

In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate by clear and convincing evidence that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

b. Discussion

According to Teva, the '942 patent, alone or in combination with a variety of prior art references, disclosed all of the limitations of claim 1 of the '830 patent. Teva argues that a motivation to combine exists inasmuch as moxifloxacin would have been "obvious to try" in a topical ophthalmic composition, due to both market pressure and the existence of "a finite number of identified, predictable solutions" to treat ophthalmic infections. (D.I. 107 at 35-36, citing *KSR*, 550 U.S. at 419) Teva further contends that the prior art predicted a topical ophthalmic composition of moxifloxacin HCl because a person of ordinary skill in the art would have reasonably expected it to have desirable antibacterial and pharmacological properties. In contrast, Alcon maintains that, in 1998, the prior art characterized moxifloxacin HCl as an undesirable and unsuitable candidate for a topical ophthalmic composition.

In *KSR*, the Supreme Court stated that "the fact that a combination was obvious to try might show that it was obvious under § 103" in certain circumstances. 550 U.S. at 420. That is,

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. Teva asserts that moxifloxacin was "obvious to try" in a topical ophthalmic composition due to both the market pressure faced by Alcon as a result of the impending expiration of the patent on ciprofloxacin and the "finite number of identified, predictable solutions" that could serve to act as a successor drug. In support of this argument, Teva emphasizes that Dr. Stroman left the 1997 ICAAC with "five or six"

candidates, among them moxifloxacin, to test for suitability as ciprofloxacin's replacement. Certainly, if the world of potential successors were limited to five or six compounds, it would be obvious to try each in a topical ophthalmic composition. However, the record indicates anything but a finite number of identified, predictable solutions. Specifically, Teva fails to consider that Dr. Stroman's search spanned years and a number of different conferences in which he likely considered thousands of abstracts. (D.I. 102 at 570-71) Dr. Stroman also indicated that, of the roughly one hundred compounds he managed to actually obtain, a majority were not quinolones. (*Id.* at 641) The numerous compounds considered by Dr. Stroman demonstrate that the universe of successor compounds was not as succinctly identified as Teva contends; indeed, the court finds that the realm of potential solutions included the myriad quinolone and non-quinolone antibacterials alike which had been disclosed by the prior art. The court, therefore, concludes that it was not "obvious to try" moxifloxacin in a topical ophthalmic composition.

Teva argues a separate theory concerning a motivation to combine. Dr. Lloyd Allen, Teva's formulation expert, testified that the substitution of moxifloxacin for the other active ingredients of prior art topical ophthalmic compositions was completely predictable in September 1998. Specifically, Dr. Allen opined that one skilled in the art would have reasonably expected that exchanging ofloxacin, the active ingredient of OCUFLOX®, or ciprofloxacin, the active ingredient of CILOXAN®, for moxifloxacin would result in a topical ophthalmic composition that displayed antibacterial properties. (D.I. 100 at 205-06; D.I. 101 at 221, 222-23) Dr. Allen posited that the motivation to make this substitution came from two discrete sources. According to Dr. Allen, both the

biological activity data contained in the 1997 Bayer ICAAC poster and the pharmacological profile disclosed by the '942 patent would have demonstrated to one skilled in the art that "an ophthalmic formulation containing moxifloxacin HCl would be a pharmaceutical composition with antibacterial properties." (D.I. 107 at 34)

While the court does not disagree with Teva's conclusion that a topical ophthalmic composition of moxifloxacin HCl would predictably possess these characteristics, the court finds that this conclusion provides little insight into a question crucial to the obviousness inquiry; namely, whether the prior art motivated a person of ordinary skill to even **select** moxifloxacin for use in a topical ophthalmic composition. *See generally Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357-62 (Fed. Cir. 2007) (no determination of obviousness where the prior art does not lead one of ordinary skill to select "compound b" as starting point); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (no determination of obviousness where the record indicated that "even if an ordinarily skilled artisan sought an FBPase inhibitor, that person would not have chosen topiramate."). Indeed, without questioning why one of ordinary skill would select moxifloxacin for this particular application, Teva avoids consideration of the prior art that taught away from the selection of moxifloxacin, including the salient commercial and regulatory realities of the drug development process.

The '830 patent provides that the field of treating and preventing ophthalmic infections was concerned with developing "improved compositions . . . based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens." (PTX

5 at col. 1, ll. 49-53) One skilled in the art would understand that this disclosure referred to the sight-threatening pathogens *Pseudomonas aeruginosa* and *Staphylococcus aureus* and the standard treatment of such by CILOXAN® and OCUFLOX®. (D.I. 101 at 381-87) A person of ordinary skill in the art would also understand that a resistance problem existed with respect to the treatment of these two key ophthalmic pathogens, and that this issue was critical to the development of a viable new treatment. It was evident in 1998 that any potential ophthalmic treatment which did not improve upon the efficacy and resistance issues would be considered impractical and worthless to one skilled in the art.

As discussed previously, when Dr. Stroman stumbled upon the 1997 Bayer ICAAC poster, the *in vitro* data for BAY 12-8039 indicated that moxifloxacin was eight times less active than ciprofloxacin against *Pseudomonas aeruginosa*. (PTX 1098) According to Dr. George Zhanel, a Professor of Medical Microbiology Infectious Diseases at the University of Manitoba, this eight-fold difference in activity is "hugely significant." (D.I. 103 at 860-61) The significance of this diminished activity arises from the quinolone class resistance problem. The treatment of *Pseudomonas aeruginosa* by a quinolone with less activity than ciprofloxacin would drive resistance to quinolones as a whole if the bacterial strains were not completely eliminated. Thus, even though moxifloxacin was more active than ciprofloxacin against *Staphylococcus aureus*, a person of ordinary skill in the art would have dismissed it in light of its poor activity against *Pseudomonas aeruginosa,* the critical intraocular pathogen.

The uncertain toxicity status of moxifloxacin would have also weighed against its development into a topical ophthalmic treatment. While the toxicity profile of a new

compound is unpredictable, quinolones, as a class, were considered extremely toxic. (D.I. 104 at 931) Dr. Zhanel explained that, as a general rule, "the more powerful the quinolones are at killing bacteria, the more powerful they are at killing people." (D.I. 103 at 897-98) Ciprofloxacin and ofloxacin, the exceptions to this rule, were considered generally safe and exhibited negligible side effects. (*Id.*) Thus, one skilled in the art would only consider viable a treatment that exhibited a similar risk profile, especially in light of the intended prophylactic use.[28]

In 1998, having just finished Phase I of the NDA process, moxifloxacin did not possess this profile. Indeed, as previously mentioned, many quinolones that successfully passed Phase I were later determined to exhibit some form of toxicity.[29] (D.I. 104 at 907-14; PTX 2025) The potential for serious adverse reactions would be unacceptable to one skilled in the art considering prophylactic treatments for low risk procedures.[30] Such apprehension is evident in the existence of several quinolones, for which promising toxicity data was available, that were not pursued as ophthalmic treatments. (D.I. 103 at 911-14) Before developing moxifloxacin into a topical ophthalmic composition, one skilled in the art would wait for further reassurance than could be provided by the successful completion of Phase I.

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[28]Dr. Eduardo Alfonso, an ophthalmologist at the Baskin-Palmer Eye Institute in Miami, explained that the predominant use was prophylactically in cataract and Lasik surgery patients, both of which exhibited a low incidence of infection. (D.I. 102 at 397)

[29]Temafloxacin and trovafloxacin, in particular, were only deemed toxic after the completion of all phases of clinical testing. (PTX 2025)

[30]Dr. Zhanel provided several examples of quinolones that, upon ophthalmic administration, could cause a potentially fatal cardiac toxicity. (D.I. 104 at 934-47)

In conducting the obviousness inquiry, the court must also consider whether the prior art, as a whole, "teaches away" from the claimed invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The Federal Circuit has explained that a reference "teaches away" if one skilled in the art, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Id.* In light of the foregoing reasons, the court concludes that both moxifloxacin's *Pseudomonas aeruginosa* resistance profile data, as well as its uncertain but probable toxicity, teach away from the invention of the '830 patent.

Drawing upon a factual background vaguely similar to the case at bar, Teva argues that the finding of obviousness with respect to the substitution of one quinolone for another in *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254 (Fed. Cir. 2007), mandates that this court reach a similar conclusion. The claims in *Daiichi* were drawn to a method of treating ear infections with a topical composition of ofloxacin. *Id.* In making the determination that the claimed invention was obvious, the Court considered a prior art reference, ignored by the trial court,[31] that taught the successful use of ciprofloxacin in a topical solution to treat middle ear infections. *Id.* at 1258. The reference explained that ciprofloxacin, a gyrase inhibitor, "would definitely have to be suitable for use as eardrops" because it lacked appreciable ototoxicity. *Id.* The Court also relied on the testimony of Apotex's expert that one skilled in the art would understand from the

[31]The trial court dismissed this teaching because it found that the reference spoke beyond what it had erroneously determined to be the level of ordinary skill in the art. *Id.*

reference that ofloxacin, also a gyrase inhibitor, "would be very likely equally effective as ciprofloxacin [sic] when used topically to treat middle ear infections" and that ofloxacin would likely also display a similar lack of ototoxicity. *Id.* Daiichi's only relevant response[32] to the teachings of this reference consisted of the "conclusory statement that [o]ne cannot extrapolate a safety profile for one antibiotic to another."[33] *Id.* at 1259.

Initially, the court notes that the fact-intensive nature of the obviousness inquiry renders it incompatible with the use of a proxy. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). Thus, a determination of the existence or absence of obviousness must rest upon the factual record of the individual case. *Id.* Regardless of this axiom, the court finds several grounds upon which to distinguish the case at bar from *Daiichi*. Importantly, the record is replete with evidence of the general tendency of quinolones, as a class, to exhibit toxic properties, thus foreclosing any claim that a person of ordinary skill would reasonably expect moxifloxacin to be as safe as ciprofloxacin. Furthermore, no expert testified that one skilled in the art would have considered moxifloxacin as effective as ciprofloxacin in treating and preventing intraocular infections. Finally, considerations unique to the field of ophthalmic treatment and prevention, such as ocular penetration and the nature of intraocular pathogens, are sufficient to create hesitation in reading too many similarities between the case at bar and another which concerned a drug delivery system directed towards the ear.

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[32]Daiichi based most of its arguments upon the trial court's improper determination of the level of ordinary skill in the art. *Id.*

[33]The Court explained that "[t]his unsupported statement cannot refute the detailed testimony of Apotex's expert." *Id.*

The court notes that several secondary considerations of nonobviousness support the conclusion that moxifloxacin was not an obvious active ingredient in a topical ophthalmic composition. The record indicates that when Alcon announced its intent to pursue moxifloxacin as an ophthalmic composition, artisans in the field were "upset" and expressed "dismay" over the investigation of another potential resistance-enhancing quinolone believed to be unsuitable for ophthalmic treatment. (D.I. 101 at 415-16) Such skepticism by experts "constitutes strong evidence of nonobviousness." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52 (1966)). In 1998, it was evident that there existed a long felt need for a compound that could more effectively treat intraocular infections of key pathogens without rapidly developing resistance. Furthermore, it is undisputed that the commercial success of VIGAMOX®, an embodiment of claim 1, has resulted in hundreds of millions of dollars in sales. (D.I. 75 at ¶ 4)

The unexpected properties of the invention are likewise probative of nonobviousness. The Federal Circuit has mandated the consideration of all relevant properties of a compound in the context of the obviousness inquiry. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006). When "unexpected" and "significant" differences exist between the properties of the claimed invention and those of the prior art, a finding of nonobviousness may be warranted. *Id.* The court finds that the ocular penetration of the topical ophthalmic solution of claim 1 is both unexpected and significant. The eye is comprised of several layers that work in unison to repel a broad spectrum of substances. (D.I. 102 at 697-705) A compound's effective diffusion into, and subsequent retention by, the eye depends upon a variety of

factors, including, inter alia, molecular weight, lipophilicity and hydrophilicity. (*Id.*) At trial, Dr. Ashim Mitra[34] testified that, in light of these factors and the data available for moxifloxacin in 1998, one skilled in the art would conclude that moxifloxacin would penetrate at a slightly lower rate than ofloxacin. (*Id.* at 710-11) Unpredictably, Alcon's tests upon moxifloxacin compositions revealed a penetration rate greater than two times that of ofloxacin. (D.I. 103 at 729; PTX 1116) Each of the claimed compositions exhibit this enhanced penetration rate throughout the concentration range of claim 1. (PTX 1116; PTX 1119)

In conclusion, the court finds no motivation to combine the teachings of the prior art to result in a topical ophthalmic composition of moxifloxacin. Rather, it is evident that the prior art consistently taught away from the use of moxifloxacin in ophthalmic treatments. Finally, several secondary considerations of nonobviousness demonstrate

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[34]Teva requests that the court exclude Dr. Mitra's testimony and accompanying exhibits (PTXs 364-66 and 1116) with respect to unexpected results for failure to comply with Fed. R. Civ. P. 26(e). During a deposition, Dr. Mitra explained that he had only examined the ocular penetration data for VIGAMOX®. (D.I. 103 at 770) At trial, it was shown that Dr. Mitra had instead examined noncommercial moxifloxacin vehicles. (*Id.*) Teva asserts that this was a material change in testimony because the nature of the vehicle can affect ocular penetration. (*Id.* at 761) Therefore, Teva argues, Alcon had an affirmative burden to supplement Dr. Mitra's expert report, and the failure to do so has resulted in prejudice against Teva.

The court initially notes that nothing material has changed with respect to the substance of Dr. Mitra's opinion, that is, that ophthalmic compositions of moxifloxacin exhibit superior ocular penetration when compared to similar compositions of ciprofloxacin and ofloxacin. Furthermore, Teva's allegation of prejudice is exaggerated. While the vehicle can certainly affect ocular penetration, the use of the same vehicle in all of the analyzed compositions will equalize any additional penetration provided by a given vehicle. Thus, it was harmless error that Dr. Mitra mistakenly believed that he had examined commercially optimized formulations when, in fact, his examination concerned noncommercial but standardized vehicles. (*Id.* at 731-32) The court finds no reason to exclude Dr. Mitra's testimony or exhibits.

that it was not obvious to incorporate moxifloxacin into such a composition. Therefore, the court finds that Teva has failed to adduce clear and convincing evidence that the invention of the '830 patent is obvious.

3. Best mode

a. Legal standard

The best mode requirement of 35 U.S.C. § 112, ¶ 1 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and **shall set forth the best mode contemplated by the inventor of carrying out his invention**.

35 U.S.C. § 112 (2002) (emphasis added).

"The purpose of the best mode requirement is to ensure that the public, in exchange for the rights given the inventor under the patent laws, obtains from the inventor a full disclosure of the preferred embodiment of the invention." *Dana Corp. v. IPC Ltd. P'ship*, 860 F.2d 415, 418 (Fed. Cir. 1988). Consequently, the best mode requirement of § 112 "requires an inventor to disclose the best mode contemplated by him, as of the time he executes the application, of carrying out the invention." *Bayer AG & Bayer Corp. v. Schein Pharms., Inc.*, 301 F.3d 1306, 1314 (Fed. Cir. 2002) (citation omitted). "The existence of a best mode is a purely subjective matter depending upon what the inventor actually believed at the time the application was filed." *Id.* Because of this subjectivity, § 112 demands actual disclosure, regardless of whether practicing that mode would be within the knowledge of one of ordinary skill in the art. *Id.* Nevertheless,

the extent of this actual disclosure is limited to the invention as defined by the claims. *Id.* at 1315.

In determining whether an inventor has disclosed the best mode, the Federal Circuit has adopted a two-step inquiry. First, the invention must be defined by construing the claims. *Id.* at 1320 (citing *Northern Telecom Ltd. v. Samsung Elec. Co.*, 215 F.3d 1281, 1286-87 (Fed. Cir. 2000)). The Federal Circuit has noted in this regard that "[d]efinition of the invention 'is a legal exercise, wherein the ordinary principles of claim construction apply.'" *Id.* It has also commented that such definition "is a crucial predicate to the factual portions of the best mode inquiry because it ensures that the finder of fact looks only for preferences pertaining to carrying out the claimed invention." *Id.*

Once the claim analysis is complete, the finder of fact may proceed to the second step and determine whether, at the time of filing the application, the inventor possessed a best mode for practicing the claimed invention. *Id.* at 1320. If the inventor subjectively contemplated a best mode, then the fact-finder must evaluate whether the inventor's disclosure is objectively adequate to enable one of ordinary skill in the art to practice the best mode of the claimed invention. *Id.*

The Federal Circuit further has delineated that "if the best mode for carrying out the claimed invention involves novel subject matter, then an inventor must disclose a method for obtaining that subject matter even if it is unclaimed." *Id.* at 1322 (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 965 (Fed. Cir. 2001)). In other words, when the subject matter is unclaimed, but both novel and essential for carrying out the best mode of the claimed invention, disclosure is required. *Id.* With regard to unclaimed

subject matter unrelated to the properties of the claimed invention, the Federal Circuit has acknowledged that an inventor need not disclose a mode for obtaining it. *Id.* (citing *Eli Lilly*, 251 F.3d at 963)

b. Discussion

As discussed previously, Dr. Stroman handled and analyzed only one form of moxifloxacin - that of moxifloxacin HCl (BAY 12-8039). Teva asserts that moxifloxacin HCl was the only mode known to and contemplated by Dr. Stroman. According to Teva, material differences in solubility, stability and tolerability exist between the salt and betaine forms of moxifloxacin. (D.I. 100 at 143; D.I. 102 at 461) Teva contends, in view of these alleged material differences, that Alcon violated the best mode requirement by failing to disclose moxifloxacin HCl in the '830 patent.

Teva relies upon *Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923 (Fed. Cir. 1990), wherein the Federal Circuit explained that a patentee's failure to disclose the only mode contemplated results in a violation of the best mode requirement. The claims at issue in *Chemcast* were drawn to a sealing member, such as a grommet, designed to seal an opening in sheet metal. The patentee failed to disclose "(1) the particular type, (2) the hardness, and (3) the supplier and trade name" of the material used to construct the sealing member, resulting in the lower court holding the patent invalid for failure to satisfy the best mode requirement. *Id.* at 926. In affirming the lower court's finding of invalidity, the *Chemcast* court noted that the patentee had selected the material, which had been custom made for the patentee, because it exhibited a desirable hardness. *Id.* at 929. The *Chemcast* court emphasized that "the only embodiment of the claimed invention known" to the patentee included this specific material. *Id.* The Court noted

that a best mode violation is especially evident "where the inventor has failed to disclose the only mode he ever contemplated . . . ." *Id.* at 930.

As an initial matter, the court disagrees with Teva's assertion that moxifloxacin HCl was Dr. Stroman's preferred embodiment. Unlike the patentee in *Chemcast* who preferred the hardness possessed by the undisclosed material, the undisputed evidence before the court indicates that Dr. Stroman held no such preference for moxifloxacin HCl.[35] This finding is supported by Dr. Stroman's testimony that he was unaware of the existence of the salt form and the corroborating correspondence between Dr. Stroman and Bayer regarding the sample of BAY 12-8039, which repeatedly evinced Dr. Stroman's (incorrect) understanding that BAY 12-8039 was nothing more than moxifloxacin betaine. Dr. Stroman's ignorance with respect to the true nature of BAY 12-8039 is understandable, given the focus of his search. Dr. Stroman based his selection upon considerations of biological activity, an invariable characteristic among the salt and betaine forms of moxifloxacin. Conversely, formulation issues such as enhanced solubility[36] were not examined by Dr. Stroman at the time that Alcon filed the '504 and '506 applications. Dr. Stroman needed only to dissolve the compound into solution form, a feat which both the betaine and salt forms are capable of across the concentration range of claim 1. (D.I. 100 at 143) Thus, it is evident from the record that

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[35]Teva has adduced no evidence showing that Dr. Stroman preferred moxifloxacin HCl over moxifloxacin betaine.

[36]Dr. Taylor testified upon cross by defendants that "HCl salts are known . . . for their solubilities." (D.I. 100 at 143)

Dr. Stroman's preferred mode was simply that of a topical ophthalmic solution containing moxifloxacin; the '830 patent fully discloses this embodiment.

Even assuming, *arguendo*, that Dr. Stroman espoused a preference for moxifloxacin HCl, Teva's asserted best mode violation is deficient because no material difference exists between the betaine and salt forms of moxifloxacin. The Federal Circuit has maintained that only "[p]references . . . [that] have a **material effect** on the properties of the claimed invention must be disclosed." *Bayer AG & Bayer Corp. v. Schein Pharms., Inc.*, 301 F.3d 1306, 1321 (Fed. Cir. 2002) (emphasis added). Teva argues that a solution comprised of moxifloxacin HCl will materially differ from a solution comprised of moxifloxacin betaine in terms of both pH and solubility. Specifically, Teva points to the testimony of Dr. Alfonso, who explained that pH can effect the ophthalmic tolerability of a solution. (D.I. 101 at 461) The pH of a solution, however, can be easily adjusted.[37] (D.I. 103 at 820) Teva also contends that the enhanced solubility of moxifloxacin HCl alleviates formulation concerns present with the betaine form. However, the betaine form still dissolves across the concentration range of claim 1, rendering these formulation concerns negligible. (D.I. 100 at 143) Therefore, the court finds that these differences do not have a material effect on the invention of claim 1.

Consequently, Teva has not produced clear and convincing evidence that Alcon failed to disclose its best mode with respect to the composition of claim 1.

4. Written description

a. Legal standard

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[37]This is known as "buffering" the solution.

35 U.S.C. § 112, ¶ 1 also requires that "[t]he specification shall contain a **written description** of the invention . . . ." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (emphasis added). The written description requirement embodies the basic disclosure function of a patent. In exchange for a limited power of exclusion, the patentee must provide to the public a "meaningful disclosure" of his invention. *See Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 922 (Fed. Cir. 2004). "To satisfy the written description requirement, 'the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" *Carnegie Mellon Univ. v. Hoffmann La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *In re Alton*, 76 F.3d 1168, 1172 (Fed. Cir. 1996)).

A patentee, however, "can lawfully claim only what he has invented and described, and if he claims more his patent is void." *O'Reilly v. Morse*, 56 U.S. 62, 121 (U.S. 1854). Indeed, "a broad claim is invalid when the entirety of the specification clearly indicates that the invention is of a much narrower scope." *Cooper Cameron Corp. v. Kvaerner Oilfield Prods.*, 291 F.3d 1317, 1323 (Fed. Cir. 2002) (explaining *Gentry Gallery v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998)). Satisfaction of the written description requirement is a fact-based inquiry, depending on "the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed." *Carnegie*, 541 F.3d at 1122.

b. Discussion

Teva asserts that claim 1 is invalid because it is directed to a composition in which a preservative is not required. According to Teva, because the specification of the

'830 patent requires the ophthalmic compositions to include a preservative, the invention of claim 1 is not sufficiently described within the meaning of 35 U.S.C. § 112, ¶ 1. Alcon responds that the specification does not require a preservative for all of the embodiments disclosed, and cites to specific examples in which preservatives are absent. Alcon contends that claim 1, therefore, is not broader than the scope afforded to it by the disclosure of the '830 patent.

The court agrees with Alcon that the disclosure of the '830 patent adequately supports a claim that does not include a separate preservative as a limitation. The '830 patent provides, in relevant part, that "[o]phthalmic . . . products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use." (PTX 5 at col. 5, l. 66-col 6, l. 9) Teva's reliance on this language to establish the necessity of a preservative is misplaced. A person of ordinary skill would interpret the quoted language to indicate that the present invention includes both multidose and single dose forms. (D.I. 101 at 311-12, 435-38, 456-57) Likewise, one skilled in the art would not understand the specification to indicate that a preservative is necessary for a single dose product. (*Id.*) Thus, the specification indicates that preservatives are required, if at all, only for a multidose form of the drug.

It is further evident from the specification that not all of the contemplated embodiments incorporate a preservative. Example 3 of the specification describes an ophthalmic composition lacking a separate preservative. (PTX 5 at col. 7, ll. 1-10) Teva argues that the court should ignore Example 3 because there is no evidence that Alcon ever made this embodiment and there is no evidence that the formulation is self preserving. Teva concludes that the court need not construe claim 1 such that it

includes an inconsistent embodiment. *See Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1136 (Fed. Cir. 2007). Teva misapplies *Sinorgchem*, which addresses the issue of whether a claim may be construed to exclude a specific embodiment; the question at bar is whether the scope of claim 1 is consistent with the disclosure of the specification. *See id.* The court, therefore, finds no reason to exclude Example 3 as instructive of the proper scope of claim 1.

In view of the fact that Alcon has shown two instances in which a preservative is unnecessary, the court finds that Teva has failed to show, by clear and convincing evidence, that the "**entirety** of the specification [of the '830 patent] clearly indicates that the invention is of a much narrower scope." *Cooper*, 291 F.3d at 1323 (emphasis added).

5. Enablement

a. Legal standard

The statutory basis for the enablement requirement, found in 35 U.S.C. § 112, ¶ 1, provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

The Federal Circuit has explained that "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and to use the full scope of the claimed invention without undue experimentation. *Genentech*, 108 F.3d at 1365. "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Id.* at 1366. The specification need not teach what is well known in the art. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The use of prophetic examples does not automatically make a patent non-enabling. The burden is on one challenging validity to show, by clear and convincing evidence, that the prophetic examples, together with the other parts of the specification, are not enabling. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

Some experimentation may be necessary in order to practice a claimed invention; the amount of experimentation, however, "must not be unduly extensive." *Id.* at 1576. The test for whether undue experimentation would have been required is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *PPG Indus. Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982)). A court may consider several factors in determining whether undue experimentation is required to practice a claimed invention,

including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (6) the predictability of the art; and (7) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors are sometimes referred to as the "Wands factors." A court need not consider every one of the Wands factors in its analysis. Rather, a court is only required to consider those factors relevant to the facts of the case. *See Amgen, Inc. v. Chugai Pharm. Co.*, Ltd., 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The enablement requirement is a question of law based on underlying factual inquiries. *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re Brana*, 51 F.3d, 1560, 1567 n.19 (Fed. Cir. 1995).

b. Discussion

Teva alleges two distinct enablement violations. Teva's first contention is premised upon the same theory as its written description argument, namely, the failure of claim 1 to include the preservative mentioned in the specification. Teva argues that this over-claiming also results in an enablement violation. *See In re Mayhew*, 527 F.2d 1229, 1233 (C.C.P.A. 1976). This argument is moot inasmuch as the court has already established that the scope of claim 1 is commensurate with the disclosure provided.

Teva also concludes that a person of ordinary skill cannot practice the full scope of claim 1 without undue experimentation. The court concludes otherwise after application of the Wands factors. With respect to both the amount of experimentation necessary and the amount of guidance disclosed, Teva emphasizes the lack of process

steps for making formulations in the '830 patent. Alcon's experts, however, have demonstrated that one skilled in the art can prepare the compositions of claim 1 without undue experimentation. Dr. Alfonso explained that it would be "routine" and "easy" for the person of ordinary skill to make the formulations of claim 1. (D.I. 102 at 554-56) Teva takes issue with Dr. Alfonso's proposed order of adding ingredients in making the claimed compositions, noting that Dr. Allen would start with water while Dr. Alfonso would add water last. (D.I. 100 at 199-200; D.I. 101 at 448-49) Without making the requisite showing that either procedure would fail, Teva interprets this conflicting evidence as indicating that the '830 patent provides insufficient guidance. This, however, does not account for the very conceivable possibility that multiple procedures may result in the claimed compositions.

The testimony of Dr. Zhanel also demonstrates that the topical ophthalmic compositions can be made without the disclosure of explicit process steps. Dr. Zhanel testified for Alcon that microbiologists likewise have the necessary formulation skills to prepare the compositions of claim 1. (D.I. 104 at 991-93) Dr. Zhanel explained that "a microbiologist, given a recipe, for example, in the '830 patent, could easily make an ophthalmic composition." (*Id.* at 993) In support of this proposition, Dr. Zhanel walked through the steps he would perform to prepare the compositions of claim 1 based only on the list of ingredients provided by the '830 patent. (*Id.* at 994-1004) He further indicated that even his graduate students, who possess less education than the person of ordinary skill, can prepare the claimed compositions. (*Id.* at 992)

Teva contends that Dr. Zhanel's testimony does not aid in determining the degree of experimentation required because his formulations are not pharmaceutically

acceptable and, thus, not within the scope of claim 1. Specifically, Teva seizes upon Dr. Zhanel's testimony that he would not allow solutions prepared by his graduate students into his eyes. (*Id.* at 1004) The court finds it unsurprising that Dr. Zhanel would not allow a solution into his eyes which was not previously proven to be nontoxic. The question, as Alcon correctly identifies, is not whether microbiologists often make pharmaceutical compositions, but rather whether they could do so based on the disclosure of the '830 patent. Dr. Zhanel resolves this issue affirmatively by stating, "I have made compositions to be suitable for the eye. Do I make them frequently? Absolutely not."[38] (*Id.* at 992)

Finally, Teva contends that, while Alcon's experts may have demonstrated how to prepare solutions, no such showing has been made with respect to the gels, ointments and suspensions also covered by claim 1. Teva correctly asserts that claim 1 must be enabled in each of these categories. *See Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 1000 (Fed. Cir. 2008). However, the burden belongs to Teva to demonstrate that the '830 patent fails to enable claim 1; thus, it is of no consequence that Alcon did not first prove that each category covered by claim 1 is enabled. *See Morton Int'l v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). Upon review of the record, Teva has

[38]Alcon asserts that one with even less education than the person of ordinary skill can make the claimed compositions with the guidance provided by the '830 patent. Ms. Kathleen Alford, a microbiologist with a master's degree employed by Alcon, allegedly prepared five compositions within the scope of claim 1 using only the disclosure of the '830 patent. (D.I. 102 at 677-85) Teva contends that this testimony, too, is inapposite to the determination of enablement, because Ms. Alford did not test the resulting composition for pharmaceutical acceptability. (*Id.* at 690) The court agrees with Teva. Because Ms. Alford failed to test for osmolality, tonicity, sterility or activity, her compositions cannot properly be characterized as "pharmaceutically acceptable" and, therefore, do not provide evidence of the enablement of claim 1.

adduced no evidence to support its contention that claim 1 is not enabled. No testimony before the court indicated that the compositions of claim 1 would be difficult or impossible to make. The court, therefore, finds that Teva has failed to show, by clear and convincing evidence, that claim 1 is invalid for lack of enablement.

IV. CONCLUSION

For the reasons discussed above, the court concludes that Alcon has proven, by a preponderance of the evidence, that Teva's ANDA product infringes the '830 patent.

Teva has failed to prove, by clear and convincing evidence, that the '830 is invalid as anticipated, obvious, or for violation of the best mode, written description or enablement requirements of 35 U.S.C. § 112, ¶ 1.

An appropriate order shall issue.

Addendum 2

October 19, 2009 Order

Alcon, Inc. et al. v. Teva Pharmaceuticals USA, Inc.,
No. 06-234-SLR (D. Del.)

A51-A51

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALCON, INC. and ALCON RESEARCH, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-234-SLR
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

ORDER

At Wilmington, this 19th day of October, 2009, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Teva's ANDA product infringes claim 1 of U.S. Patent No. 6,716,830.

2. Teva has failed to prove the invalidity of U.S. Patent No. 6,716,830 by clear and convincing evidence.

3. The Clerk of Court is directed to enter judgment in favor of plaintiffs and against defendant.

United States District Judge

Addendum 3

October 20, 2009 Judgment in a Civil Case

Alcon, Inc. et al. v. Teva Pharmaceuticals USA, Inc.,
No. 06-234-SLR (D. Del.)

A52-A52

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALCON, INC. and ALCON RESEARCH, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-234-SLR
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

JUDGMENT IN A CIVIL CASE

For reasons stated in the court's memorandum opinion and order of October 19, 2009;

IT IS ORDERED AND ADJUDGED that judgment be and is hereby entered in favor of plaintiffs Alcon, Inc. and Alcon Research, Ltd. and against defendant Teva Pharmaceuticals USA, Inc.

United States District Judge

Dated: 10/20/09

(By) Deputy Clerk

Addendum 4

August 5, 2010 Memorandum Order

Alcon, Inc. et al. v. Teva Pharmaceuticals USA, Inc.,
No. 06-234-SLR (D. Del.)

A53-A58

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALCON, INC. and ALCON RESEARCH, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-234-SLR
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

MEMORANDUM ORDER

At Wilmington this 5th day of August, 2010, having reviewed plaintiff's motion for an amended judgment order (D.I. 126) and the papers submitted in connection therewith;

IT IS ORDERED that plaintiff's motion is granted in part and denied in part, as follows:

1. **Background**. The present motion arises out of a patent infringement action involving U.S. Patent No. 6,716,830 ("the '830 patent"), belonging to plaintiffs Alcon, Inc. and Alcon Research, Ltd. (collectively, "Alcon"). The '830 patent issued from PCT application US 99/22622, which was filed on September 29, 1999. (D.I. 79, ex. 1 at ¶ 17) Alcon brought its suit against Teva on April 5, 2006, alleging infringement pursuant to 35 U.S.C. § 271(e)(2)(A).[1] (D.I. 1) Alcon asserted that Teva's Abbreviated New Drug Application ("ANDA") No. 78-073, filed on or about December 25, 2005 (D.I. 79, ex. 1 at

[1]"(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

¶ 30), infringed the '830 patent, which covers a topical ophthalmic solution comprised of the active ingredient moxifloxacin hydrochloride. (D.I. 1, Ex. C)

2. In an opinion dated October 19, 2009, the court found that claim 1 of the '830 patent was valid and infringed. (D.I. 122) In its October 19, 2009 order (D.I. 12), the court instructed the Clerk of Court to enter final judgment in favor of Alcon, but did not order injunctive relief or an FDA approval date for Teva's ANDA. Presently before the court is Alcon's motion to amend the judgment (D.I. 126) pursuant to Federal Rule of Civil Procedure 60(a),[2] requesting a declaration of the effective date of ANDA No. 78-073 under 35 U.S.C. § 271(e)(4)(A) and the entry of a permanent injunction under 35 U.S.C. § 271(e)(4)(B).

3. **Effective Date**. As a preliminary matter, Alcon is entitled to a declaration that the Food and Drug Administration ("FDA") may not approve Teva's ANDA prior to March 30, 2020. Under section 271(e)(4)(A) of Title 35, when the filing of an ANDA is found to be an infringing act, "the court **shall** order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." (emphasis added) The '830 patent expires twenty years after the September 29, 1999 filing date of its parent

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[2]Corrections Based on Clerical Mistakes; Oversights and Omissions. The court may correct a clerical mistake or a mistake arising from oversight or omission whenever one is found in a judgment, order, or other part of the record. The court may do so on motion or on its own, with or without notice. But after an appeal has been docketed in the appellate court and while it is pending, such a mistake may be corrected only with the appellate court's leave.

Fed. R. Civ. P. 60(a).

application. (D.I. 79, ex. 1 at ¶ 17); 35 U.S.C. § 154. Thus, the court must order that the FDA not approve Teva's ANDA prior to the September 29, 2019 expiration date of the '830 patent. In addition, Alcon was granted a pediatric exclusivity period for six months following expiration of the '830 patent. 21 U.S.C. § 355a(c)(1)(B)(ii); *see AstraZeneca AB v. Impax Laboratories, Inc.*, 490 F. Supp. 2d 368, 371 (S.D.N.Y. 2007) (describing the requirements for receiving market exclusivity for pediatric testing). "If the drug is the subject of a Paragraph IV certification 'and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under [21 U.S.C. § 355(j)(5)(B)] shall be extended by a period of six months after the date the patent expires (including any patent extensions).'" *Id.* at 372 (citing 21 U.S.C. § 355a(c)(2)(B)). Accordingly, it is appropriate for the court to order that the FDA not approve ANDA No. 78-073 until March 30, 2020.

4. **Injunctive Relief**. Alcon asserts that it is entitled to injunctive relief under 35 U.S.C. § 271(e)(4)(B), which states, "injunctive relief **may** be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product" (emphasis added); *see Voda v. Cordis Corp.*, 536 F.3d 1311, 1329 (Fed. Cir. 2008) (affirming the denial of a permanent injunction where generic drug manufacturer lost infringement decision). In order to establish that an injunction is warranted, a plaintiff must demonstrate: "(1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the

plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). "The decision to grant or deny permanent injunctive relief is an act of equitable discretion by the district court, reviewable on appeal for abuse of discretion." *Id.* (citing *Weinberger v. Romero-Barcelo*, 456 U.S. 305, 311-13 (1982)). In the case at bar, the court must determine whether to enjoin Teva from the "commercial manufacture, use, offer for sale, or sale within the United States or importation into the United States of" the moxifloxacin opthalmic solution covered by the '830 patent. 35 U.S.C. § 271(e)(4)(B).

5. Alcon's assertion that it is entitled to a permanent injunction is seriously undermined by its failure to prove that it has suffered irreparable harm. Alcon's sole argument in this respect is that any deprivation of its right to exclude others constitutes irreparable harm to the monopoly granted by the '830 patent. This argument is unavailing. *See eBay*, 547 U.S. at 392 (holding that a patentee's "statutory right to exclude alone [does not justify] [a] general rule in favor of permanent injunctive relief," and that "injunctive relief 'may' issue only 'in accordance with the principles of equity.'") (citations omitted). Alcon cites two cases to support its irreparable harm argument. Both are inapposite. In *Martek Biosciences Corporation v. Nutrinova Incorporated*, 520 F. Supp. 2d 537 (D. Del. 2007), *aff'd in part*, 579 F.3d 1363 (Fed. Cir. 2009), the court found irreparable harm where the patentee spent $60 million to acquire the patents-in-suit, lost market share to the defendant, and attributed a commercial value to the right to exclude within the food and beverage industry. 520 F. Supp. 2d at 558. In a pre-*eBay* decision, *Honeywell International, Incorporated v. Universal Avionics Systems*

Corporation, 397 F. Supp. 2d 537 (D. Del. 2005), the court presumed irreparable harm based on the infringement of a direct competitor. 397 F. Supp. 2d at 545. Neither case supports Alcon's argument with respect to irreparable harm. Because of the relief requested under 35 U.S.C. § 271(e)(4)(A), *supra*, Teva will not be able to market its proposed moxifloxacin opthalmic product prior to the day six months after the expiration of the '830 patent, which necessarily prevents Teva from usurping any market share or goodwill from Alcon. Further, any use of the patented drug by Teva must be private and non-commercial and, therefore, cannot irreparably harm Alcon's "full enjoyment and protection of [its] patent rights." *Id.* Accordingly, Alcon cannot establish irreparable harm sufficient to satisfy the first permanent injunction factor.

6. Similarly, Alcon cannot prove that remedies available at law are inadequate to compensate for Teva's infringement. Again, Alcon rests solely on the argument that an injunction is required to repair the harm caused by the deprivation of its right to exclude. As discussed above, a remedy exists under 35 U.S.C. § 271(e)(4)(A) which prevents the FDA from approving Teva's ANDA until March 30, 2020. This effectively precludes practice of the '830 patent outside of the context of experimentation by any person or entity except for Alcon until after the patent's expiration. *See Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1133 n.2 (Fed. Cir. 1995) (referring to pediatric exclusivity period as "statutory bar" against FDA approval of ANDA). Once the '830 patent has expired, Teva may practice the invention, but will still have to wait six months before it can bring a product to market. 35 U.S.C. § 271(e)(4)(A). Without more, Alcon cannot prove that an adequate remedy at law does not exist.

7. Alcon has not met its burden in establishing that the balance of hardships tips

in its favor if injunctive relief is denied. Alcon merely asserts that the entry of an injunction maintains the status quo because the pediatric exclusivity period prevents Teva from marketing its drug until six months after the expiration of the '830 patent. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1361-63 (Fed. Cir. 2008). Alcon does not assert that it will experience any hardship beyond the deprivation of its right to exclude Teva from experimental use of the '830 patent. At most, this factor is neutral to both parties.

8. Finally, Alcon cannot show that the public interest will suffer if a permanent injunction is not entered. Although there is a "significant public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents," *id.*, enjoining Teva from use of the '830 patent does not "promote the Progress of . . . useful Arts." U.S. CONST. art. I, § 8, cl. 8. On the contrary, because Teva cannot market its drug during the term of the patent, the only effect of an injunction would be to deprive the public of the benefit of Teva's developmental efforts. Because Alcon has not shown irreparable harm, the incentives provided "to inventors to risk the often enormous costs in terms of time, research, and development," are not implicated here. *Abbott Labs.*, 544 F.3d at 1363. Accordingly, the equities weigh in favor of Teva.

9. **Conclusion**. In view of the foregoing, Alcon's request for a permanent injunction is denied. An amended order shall issue.

United States District Judge

Addendum 5

Certified Copy of United States Patent No. 6,716,830

A63-A70

PLAINTIFF'S EXHIBIT 5

D 7100809

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 06, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *6,716,830*

ISSUE DATE: *April 06, 2004*

By Authority of the

Under Secretary of Commerce for Intellectual Property

and Director of the United States Patent and Trademark Office

M. Tarver

M. TARVER

Certifying Officer

BA001-000009

US006716830B2

(12) **United States Patent**
Cagle et al.

(10) **Patent No.: US 6,716,830 B2**
(45) **Date of Patent: Apr. 6, 2004**

(54) **OPHTHALMIC ANTIBIOTIC COMPOSITIONS CONTAINING MOXIFLOXACIN**

(75) Inventors: **Gerald Cagle**, Fort Worth, TX (US); **Robert L. Abshire**, Fort Worth, TX (US); **David W. Stroman**, Irving, TX (US); **John M. Yanni**, Burleson, TX (US)

(73) Assignee: **Alcon, Inc.**, Hunenberg (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/200,868**

(22) Filed: **Jul. 22, 2002**

(65) **Prior Publication Data**

US 2002/0193370 A1 Dec. 19, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/646,797, filed as application No. PCT/US99/22622 on Sep. 29, 1999, now abandoned.

(60) Provisional application No. 60/102,506, filed on Sep. 30, 1998, and provisional application No. 60/102,504, filed on Sep. 30, 1998.

(51) **Int. Cl.**[7] **A61K 31/58**; A61K 31/44

(52) **U.S. Cl.** **514/171**; 514/230.2; 514/230.5; 514/300; 514/312; 514/913

(58) **Field of Search** 514/230.2, 230.5, 514/312, 300, 913, 171

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Primary Examiner—Zohreh Fay
(74) *Attorney, Agent, or Firm*—Gregg C. Brown

(57) **ABSTRACT**

Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues.

14 Claims, No Drawings

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OPHTHALMIC ANTIBIOTIC COMPOSITIONS CONTAINING MOXIFLOXACIN

This application is a continuation of U.S. application Ser. No. 09/646,797 filed Sep. 22, 2000 now abandoned, which is the National Stage of International Application No. PCT/US99/22622, filed Sep. 29, 1999, which claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application Nos. 60/102,504 and 60/102,506 both filed Sep. 30, 1998.

BACKGROUND OF THE INVENTION

The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class of antibiotics. The compositions of the present invention may also contain one or more anti-inflammatory agents.

The use of quinolone antibiotics to treat infections represents the current state of the art in the field of ophthalmic pharmaceutical compositions and methods of treatment. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN™ (Ciprofloxacin 0.3%) Ophthalmic Solution. The following quinolones have also been utilized in ophthalmic antibiotic compositions:

Quinolone	Product	Manufacturer
Ofloxacin	OCUFLOX ™	Allergan
Norfloxacin	CHIBROXIN ™	Merck
Lomefloxacin	LOMEFLOX ™	Senju

The foregoing quinolone antibiotic compositions are generally effective in treating ophthalmic infections, and have distinct advantages over prior ophthalmic antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which are primarily useful against gram negative pathogens; and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the ophthalmic quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

There is an even greater need for effective topical compositions and methods for treating otic and nasal infections, particularly bacterial infections. The use of oral antibiotics to treat otic infections in children has limited efficacy, and creates a serious risk of pathogen resistance to the orally administered antibiotics.

Ophthalmic, otic and nasal infections are frequently accompanied by inflammation of the infected ophthalmic, otic and nasal tissues and perhaps even surrounding tissues. Similarly, ophthalmic, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for ophthalmic, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

SUMMARY OF THE INVENTION

The invention is based on the use of a potent new class of antibiotics to treat ophthalmic, otic and nasal infections, as well as the prophylactic use of these antibiotics following surgery or other trauma to ophthalmic, otic or nasal tissues. The compositions of the present invention may also be administered to the affected tissues during ophthalmic, otic or nasal surgical procedures to prevent or alleviate post-surgical infection.

The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of ophthalmic, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to ophthalmic, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to ophthalmic, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

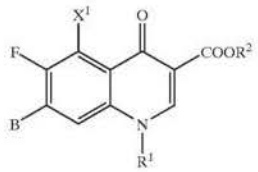
Examples of otic conditions that may be treated with the compositions of the present invention include otitis externa and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

The compositions of the present invention are specially formulated for topical application to ophthalmic, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic, otic and nasal tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other physical conditions.

DETAILED DESCRIPTION OF THE INVENTION

The antibiotics used in the compositions and methods of the present invention have the following formula:

(I)



wherein:

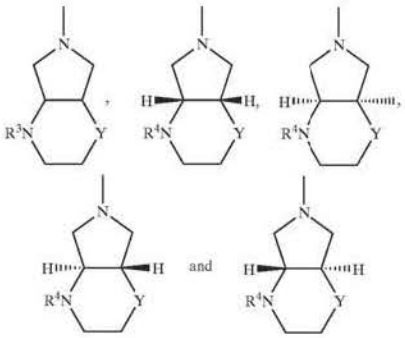
A is CH, CF, CCl, C—OCH_3, or N;

X^1 is H, halogen, NH_2, or CH_3;

R^1 is C_1 to C_3 alkyl, FCH_2CH_2, cyclopropyl or phenyl, optionally mono-, di- or tr-substituted by halogen, or A R_1 together can form a bridge of formula C—O—CH_2—$CH(CH_3)$;

R^2 is H, C_1 to C_3 alkyl (optionally substituted by OH, halogen or NH_2), or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is a selected from the group consisting of:



wherein:

Y is O or CH_2;

R^3 is C_2–C_5 alkoxyl, CH_2—CO—C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$—CH=C—CO_2R', CH=CH—CO_2R' or CH_2CH_2—CN,

wherein:

R' is H or C_1 to C_3 alky;

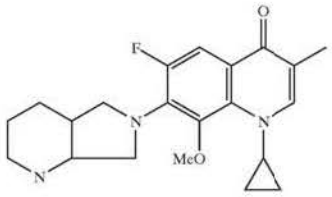
R^4 is H, C_1 to C_3 alkyl, C_2–C_5 alkoxyl, CH_2-CO—C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$—CH=C—CO_2R', CH=CH—CO_2R', CH_2CH_2—CN or 5-methyl-2-oxo-1,3dioxol-4-yl-methyl,

wherein:

R' is H or C_1 to C_3 alkyl; and

their pharmaceutically useful hydrates and salts.

The compound Moxifloxacin is most preferred. Moxifloxacin has the following structure:



Further details regarding the structure, preparation, and physical properties of Moxifloxacin and other compounds of formula (I) are provided in U.S. Pat. No. 5,607,942.

The concentrations of the antibiotics of formula (I) in the compositions of the present invention will vary depending on the intended use of the compositions (e.g., treatment of existing infections or prevention of post-surgical infections), and the relative antimicrobial activity of the specific antibiotic selected. The antimicrobial activity of antibiotics is generally expressed as the minimum concentration required to inhibit the growth of a specified pathogen. This concentration is also referred to as the "minimum inhibitory concentration" or "MIC". The term "MIC90" refers to the minimum concentration of antibiotic required to inhibit the growth of ninety percent (90%) of the strains of a species. The concentration of an antibiotic required to totally kill a specified bacteria is referred to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Moxifloxacin for several bacteria commonly associated with ophthalmic, otic and nasal infections are provided in the following table:

Microorganism	MIC_{90}
S. aureus/methicillin sensitive	0.13
S. aureus/methicillin resistant	4.0
S. aureus/quinolone resistant	4.0
S. epidermidis/methicillin sensitive	0.25
S. epidermidis/methicillin resistant	4.0
S. pneumoniae/penicillin sensitive	0.25
S. pneumoniae/penicillin resistant	0.25
P. aeruginosa	8.0
H. influenzae/β-lactamase positive	0.06
H influenzae/βlactamase negative	0.06

All of the foregoing concentrations are expressed as micrograms per milliliter ("mcg/ml").

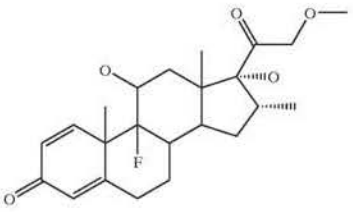
The appropriate antibiotic concentration for ophthalmic compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC90 level for the selected antibiotic (s), relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the infected tissues equal to or greater than the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with otic or nasal infections. Such amounts are referred to herein as "an antimicrobial effective amount". The compositions of the present invention will typically contain one or more compounds of formula (I) in a concentration of from about 0.1 to about 1.0 percent by weight ("wt. %") of the compositions.

The compositions of the present invention may also contain one or more anti-inflammatory agents. The anti-inflammatory agents utilized in the present invention are broadly classified as steroidal or non-steroidal. The preferred steroidal anti-inflammatory agents are glucocorticoids.

The preferred glucocorticoids for ophthalmic and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

The dexamethasone derivatives described in U.S. Pat. No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to compositions for treating ophthalmic inflammation. The following compounds are especially preferred:

AL-1529



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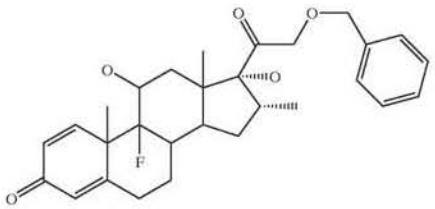
AL-2512



These compounds are referred to herein as "21-ether derivatives of dexamethasone". The 21-benzyl ether derivative (i.e., compound AL-2512) is particularly preferred.

The preferred non-steroidal anti-inflammatory agents are: prostaglandin H synthetase inhibitors (Cox I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib, P54, etodolac, L-804600 and S-33516; PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFκB transcription factor; or other anti-inflammatory agents known to those skilled in the art.

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted ophthalmic, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein as "an anti-inflammatory effective amount". The compositions of the present invention will typically contain one or more anti-inflammatory agents in an amount of from about 0.01 to about 1.0 wt. %.

The compositions are typically administered to the affected ophthalmic, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable amount of an ointment, gel or other solid or semisolid composition, one to four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected ophthalmic, otic or nasal tissues during surgical procedures.

The ophthalmic, otic and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one or more anti-inflammatory agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The ophthalmic compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and ophthalmic tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram of water ("mOsm/kg"), but will preferably be about 300 mOsm/kg.

Ophthalmic, otic and nasal pharmaceutical products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

The use of viscosity enhancing agents to provide the compositions of the invention with viscosities greater than the viscosity of simple aqueous solutions may be desirable to increase ocular absorption of the active compounds by the target tissues or increase the retention time in the eye, ear or nose. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The following examples are provided to further illustrate the ophthalmic, otic and nasal compositions of the present invention.

EXAMPLE 1

Ophthalmic/Otic/Nasal Solution

Ingredient		Amount (wt. %)
Moxifloxacin		0.35
Sodium Acetate		0.03
Acetic Acid		0.04
Mannitol		4.60
EDTA		0.05
Benzalkonium Chloride		0.006
Water	q.s.	100

EXAMPLE 2

Ophthalmic/Otic/Nasal Suspension

Ingredient	Amount (wt. %)
Moxifloxacin	0.3
Dexamethasone, Micronized USP	0.10
Benzalkonium Chloride	0.01
Edetate Disodium, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or Sodium Hydroxide, NF	q.s. for pH adjustment to 5.5
Purified Water, USP	q.s. to 100

EXAMPLE 3

Ophthalmic Ointment

Ingredient	Amount (wt. %)
Moxifloxacin	0.35
Mineral Oil, USP	2.0
White petrolatium, USP q.s	100

EXAMPLE 4

Ophthalmic Ointment

Ingredient	Amount (wt. %)
Moxifloxacin	0.3
Fluorometholone Acetate, USP	0.1
Chlorobutanol, Anhydrous, NF	0.5
Mineral Oil, USP	5
White Petrolatum, USP q.s.	100

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

What is claimed is:

1. A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt % and pharmaceutically acceptable vehicle therefor.

2. An ophthalmic composition according to claim **1**, wherein the composition further comprises an anti-inflammatory effective amount of a steroidal or non-steroidal glucocorticoid.

3. An ophthalmic composition according to claim **2**, wherein the anti-inflammatory agent comprises a steroidal agent.

4. An ophthalmic composition according to claim **3**, wherein the steroidal agent comprises a glucocorticoid.

5. An ophthalmic composition according to claim **4**, wherein the glucocorticoid is selected from the group consisting of dexamethasone, rimexolone, prednisolone, fluorometholone, hydrocortisone, mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

6. An ophthalmic composition according to claim **4**, wherein the glucocorticoid comprises dexamethasone.

7. An ophthalmic composition according to claim **4**, wherein the glucocorticoid comprises a 21-ether derivative of dexamethasone.

8. An ophthalmic composition according to claim **4**, wherein the glucocorticoid comprises a 21-benzyl ether derivative of dexamethasone.

9. An ophthalmic composition according to claim **2**, wherein the anti-inflammatory agent comprises a non-steroidal agent selected from the group consisting of prostaglandin H synthetase inhibitors, cyclooxygenase type II selective inhibitors, PAF antagonists, and PDE IV inhibitors.

10. An ophthalmic composition according to claim **9**, wherein the non-steroidal agent comprises a prostaglandin H synthetase inhibitor.

11. An ophthalmic composition according to claim **10**, wherein the prostaglandin H synthetase inhibitor comprises nepafenac.

12. An ophthalmic composition according to claim **10**, wherein the prostaglandin H synthetase inhibitor comprises ketorolac.

13. An ophthalmic composition according to claim **10**, wherein the prostaglandin H synthetase inhibitor comprises diclofenac.

14. An ophthalmic composition according to claim **9**, wherein the non-steroidal agent comprises a cyclooxygenase type II selective inhibitor.

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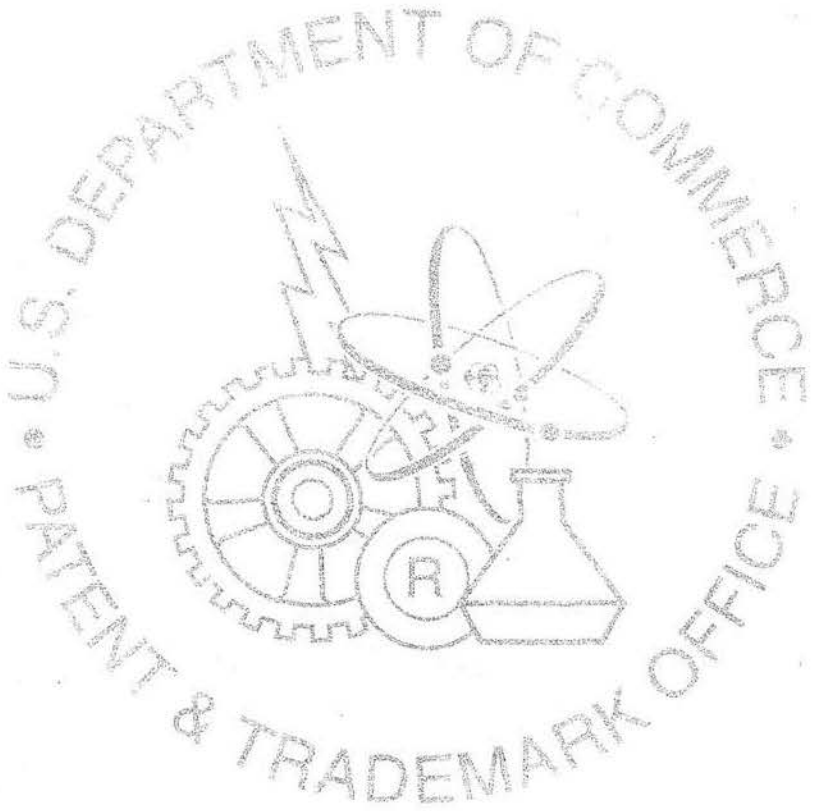
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